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Metalation of the Di- and Tri-Methoxybenzenes

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METALATION OF THE DI- AND TRI-METHOXYBENZENES

A Thesis

Presented to

the Faculty of the Department of Chemistry

Western Kentucky University

Bowling Green, Kentucky

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

by

Phillip Andrew Shelton

August 2001

METALATION OF THE DI- AND TRI-METHOXYBENZENES

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METALATION OF THE DI- AND TRI-METHOXYBENZENES

Phillip Andrew Shelton August 2001 84 Pages

Directed by: Donald Slocum, Robert Holman and Lester Pesterfield

Department of Chemistry Western Kentucky University

Hydrocarbon solvents are known to be unreactive towards organolithium reagents and also to afford little support for ortho-metalation reactions. In contrast, both m- and o-dimethoxybenzene afford 80% "ion-multiple specific" monometalation in hydrocarbon solvent (n-hexane, cyclohexane, toluene) without the addition of any catalyst (ether or amine). These observations are, in part, attributed to the 1,2- and 1,3- formation of the n-BuLi dimer, the most reactive form of n-BuLi. In other words these substrates are acting in a "substrate-catalyzed" manner. Extensions of these concepts to 1,2,3-, 1,2,4- and 1,3,5-trimethoxybenzenes have led to further unusual observations. In particular, the 1,2,3-system affords an interesting nucleophilic aromatic substitution reaction. This autocatalytic mode of ortho-metalation offers additional insight into the controversy regarding the participation of a dimer intermediate in the mechanism of the directed ortho-metalation reaction.

I. INTRODUCTION

A. Background

A significant goal in the chemical industry is to constantly improve existing synthetic processes in order to economically produce a higher yield of product. On some occasions a production procedure has been completely changed in favor of a more cost-efficient process. This is not yet the case for the substitution of an aromatic ring. For the past century, electrophilic aromatic substitution (EAS) has been the primary method used to substitute aromatic compounds. This introduction will focus upon an alternative method of aromatic substitution, directed ortho-metalation (DoM), which offers certain advantages over the classical EAS reaction.

One of the disadvantages of the EAS procedure is the harsh nature of the reaction conditions.[1,2] Fuming nitric/sulfuric acid , Br_2, Cl_2, and $AlCl_3$ are typical reagents that often serve as their own media for a reaction of this type. The media used in metalation systems are volatile but are otherwise much less hazardous than the media necessary for EAS. The most hazardous materials used in DoM reactions are alkyllithiums which are water and air sensitive. A second advantage is that the DoM procedure affords a single product, whereas the product from an EAS reaction may contain a mixture of isomers depending on the nature of the directing group.[2,3] Of the two types of directors in an EAS reaction, meta-directors and ortho-/para-directors, it is the latter that will give a mixture of ortho- and para-substitution products. Such mixtures inevitably hinder

production because of the necessity of isolating the desired isomer. A partial solution to this problem lies in the directed ortho-metalation reaction (DoM). This reaction eliminates the problem of ortho-/para-mixtures, because it will always yield a regiospecific product ortho- to the directing metalation group(DMG).[4]

The DoM protocol is not the only aromatic substitution process that can be used to obtain regiospecifically substituted arene products. Nucleophilic aromatic substitution, halogen-metal exchange, Grignard formation and transition-metal catalyzed coupling reactions are also pathways for making arene compounds without any mixture problems. These, though, all require the use of pre-substituted benzenes, usually halobenzenes. For example, the halogen-metal exchange can be used to put a specific substituent on a ring, but the requisite aryl halide must be available or separately synthesized. Only DoM[4] and EAS[5a,b] reactions involve a direct replacement of a hydrogen atom on an aromatic ring.

B. History of the DoM Reaction

In a DoM reaction a regiospecific Li/H exchange can be effected directly on an aromatic ring. This exchange takes place ortho to a directing group, hence the name directed "ortho" metalation. The resulting lithio-intermediate can then be used in a wide variety of substitution and addition reactions. The utility of this process has grown dramatically since it was first observed. In 1939-1940 the DoM reaction was independently discovered and investigated by two renowned chemists, Henry Gilman and George Wittig.[6] They both observed that treatment of anisole with an organolithium reagent resulted in the production of a high yield of o-lithioanisole.

Roberts and Curtin were also early workers in the metalation field.[7] They were the first scientists to suggest that the DMG is coordinated to the alkyllithium reagent as

part of the reaction sequence. They speculated that substrates such as anisole coordinate to the alkyllithium reagent through the electron rich oxygen of the methoxy group. An observation reported in this same paper involved an effect whereby strong electron withdrawing, non-coordinating groups also provided an increase in ortho-metalation. Such groups provide meta-substitution in EAS procedures, so this observation represented an important regiochemical distinction.

As the metalation field began to grow, various substituents were examined to determine their efficiency as ortho-directors. The first substrates examined were aromatics with oxygen containing substituents, e.g., ethers, acetals, etc. Analogous nitrogen containing substituents were examined later. A major contribution to this area was made in the 1960's by Hauser and coworkers who found dimethylbenzylamines[8] and N-methyl-benzamides[9] could be ortho-metalated in significant yields.

DoM chemistry has been reviewed in an effort to make all the papers involving specific types of investigations available to the researcher. Review articles are invaluable to the chemist; therefore, numerous reviews of the directed ortho-metalation reaction have been published. The first such review article was written by Gilman and summarized all metalation activity through 1952.[10] Metalation chemistry was still in its infancy; therefore that review was not very extensive. Subsequently, Mallan and Bebb brought together journal articles dealing with metalations from 1952 to 1962.[11] The reviews by Gilman and Mallan and Bebb are somewhat out of date but set the standard for later articles. The most extensive review article to date was compiled by Gschwend and Rodriguez.[12] These chemists undertook the task of covering all metalation chemistry (excluding ferrocenes) up to the year 1979. While not totally exhaustive, this chapter

goes a long way in gathering all metalation information in one place. A review article was published by Professor Victor Snieckus in 1990, but this paper examined only metalation of the tertiary amide and O-carboxamide DMG's. There have been no recent review articles of metalation chemistry as a whole. In fact, the field has become so widespread that it is likely only segments of the field will be reviewed at any one time.

C. The DoM Reaction

How successful a metalation will be is affected by both external and internal factors. Internal factors are electronic and structural effects exhibited by the substrate itself, whereas external factors encompass all of the reaction conditions utilized for a metalation system. The four external factors in metalation are interrelated and consist of the identity and oligomeric structure of the alkyllithum reagent, as well as effects contributed by solvent, catalyst, and temperature.

Due to rapid increase in the synthesis of organic polymers, the use of alkyllithium reagents became commonplace making it convenient for metalation chemists to also use alkyllithiums in reactions.[13] In fact, the use of organolithiums in organic synthesis has grown significantly in the past three decades.[12,14,15] n-Butyllithium, phenyllithium, hexyllithium and heptyllithium are just a few of the different types of organolithiums available for use in the laboratory.

Among these, n-BuLi is the current reagent of choice. n-BuLi has the ability to aggregate into three different olgimer structures: dimer, tetramer, and hexamer.[16,17,18] With the various oligomer structures of n-BuLi possessing different reactivities, the solvent/catalyst system proves to be the key to shifting the equilibrium towards a specific oligomeric structure. Therefore, the emerging hypothesis that the reactivity of

organolithium reagents was related to the equilibria involving these various oligomers enabled chemists to begin to maximize the reaction's efficiency.

Speculation has moved to certainty that the dimer is the most reactive form of n-BuLi.[17b,c] Both the type of solvent and species of catalyst alter the oligomer structure. In ether, n-BuLi exhibits a tetrameric structure.[17] Non-polar, hydrocarbon solvents support a hexameric structure,[16] but when THF is the exclusive solvent a mixture of the dimer and tetramer structures is present. Recently, low temperature NMR studies have shown exclusive formation of dimeric n-BuLi in the presence of stochiometric amounts of TMEDA in toluene-d_8 (Figure 1).[19] Subsequently, Collum showed that the dimer is

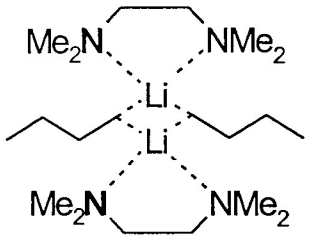


Figure 1. n-BuLi dimer formation with TMEDA catalyst.

formed in a >20:1 ratio over any other oligimer structure in toluene-d_8 when TMEDA is added.[20] Since the presence of TMEDA accelerates the rate of metalation in both hydrocarbon[21] and ether[22] solvents, the inference that the dimer form is responsible for the observed acceleration appears logical. However, this cause and effect for ortho-metalation has never actually been demonstrated.

Solvents can also affect metalation conditions in other ways. Common solvents are either commercial ethers or hydrocarbons. As a whole, the ether solvents (diethylether, MTBE, and THF) have lower boiling points than typical hydrocarbon

solvents (hexane, cyclohexane and toluene). Although elevated temperatures are not often utilized for metalation reactions, higher yields can be attained using this variable. For such reactions hydrocarbon solvents are preferable since they can support higher temperatures. In addition, hydrocarbon solvents do not react with alkyllithium reagents, a significant problem encountered with ether solvents. A study of the half-lives of various BuLi's in ether solvents has been published by Stannety *et al.* revealing significant ether instability, particularly in the presence of TMEDA.[23]

As previously stated, internal factors affecting DoM reactions are effects induced by the substrate. One internal factor is structual hindrance to DMG coordination and/or transition state formation, i. e., steric effects. These effects are not quite as dramatic in metalation reactions as they are in some other transformations, e. g., Sn_2 substitutions, but they can also make a difference as shown in research done by Melis *et al.*(Figure 2).[24] Here the DMG is part of the molecule that causes the steric hindrance. Melis *et al.* show that having large R groups on the DMG will slow metalation ortho- to that group. It has also been demonstrated that bulky substituents ortho- to the director will sterically retard the reaction.[25] In Figure 2, it can be seen that a *t*-butyl group ortho- to the director will give a 33% yield. This percentage is significantly lower than normal yields for anisole under the same conditions. It must be kept in mind that there is only one open ortho-position rather than two in an ortho-substituted anisole; this factor should decrease the rate of metalation but not necessarily the extent of metalation.

A second internal factor affecting ortho-metalation involves electronic effects between the aryl ring and the DMG. σ-Electron withdrawal by the DMG is one of those effects. Since the key to successful metalation is a smooth lithium hydrogen exchange,

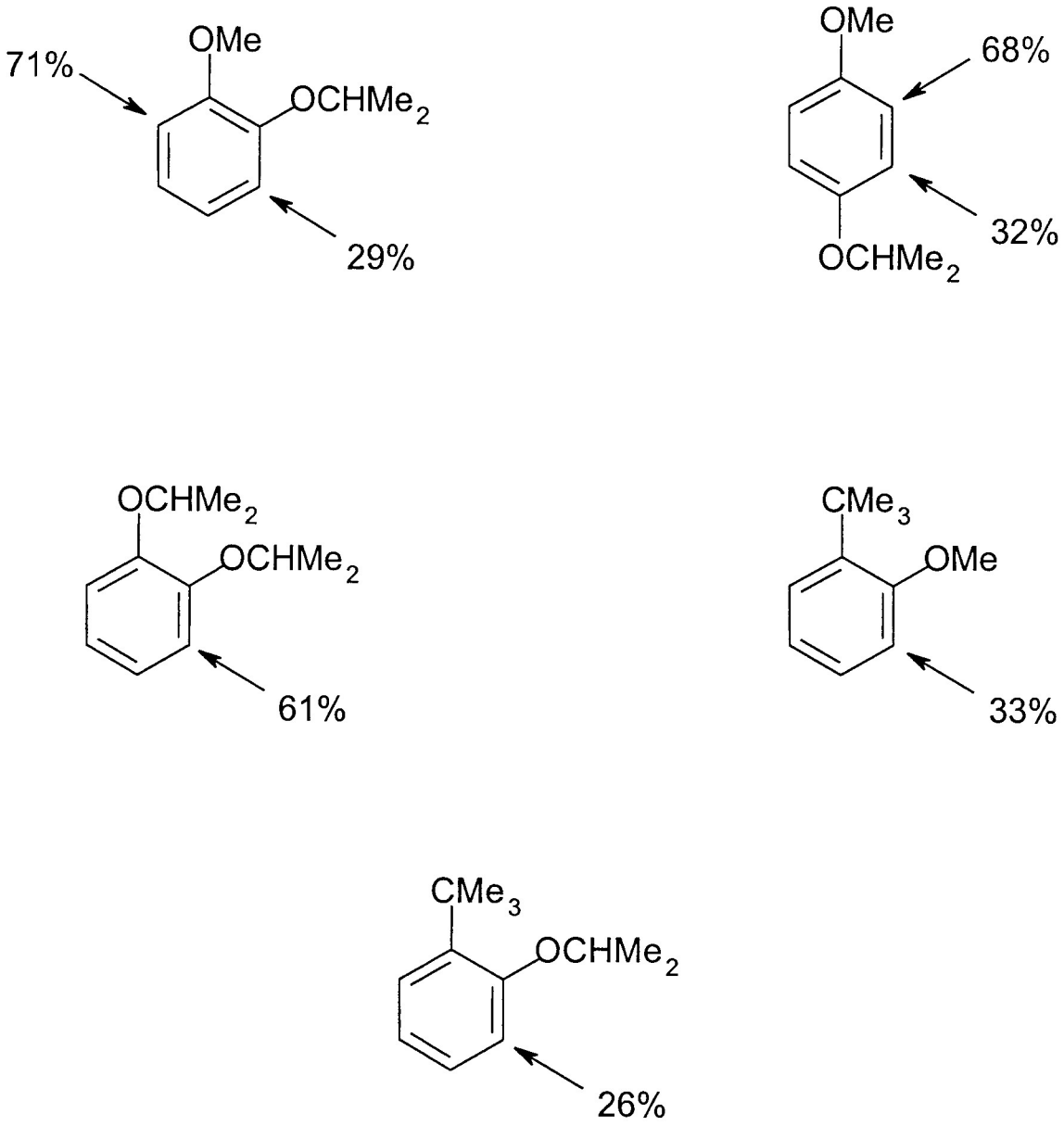


Figure 2. Effect of steric bulk at either the ether oxygen or the ortho-position of various substituted alkylarylethers.

the strength of the ortho C-H bond becomes a factor. The more withdrawing the DMG the more electron density is pulled away from the ortho-hydrogen. This effect renders that hydrogen more acidic and facilitates lithium-hydrogen exchange.[26] A second electronic effect comes from the extent of π-donation to the ring by the DMG. When a substituent is able to donate π-electrons into the aromatic ring system its lone pair(s) are not as available for coordination to the organolithium reagent.[27] A second result is an increase in π-electron density at the ortho-position(s). For the complex-induced proximity effect (CIPE) to operate, the complexing ability of the DMG to the n-BuLi dimer must be strong.

Since the lithio-intermediate is unstable it must be reacted with a trapping agent for further analysis of the product. The type of trapping agent utilized depends on the type of analysis to be performed. For instance, if the product is to be isolated a good quenching technique is carbonation, which affords a solid carboxylic acid derivative. On the other hand, if H^1 NMR analysis is anticipated, a D_2O quench is useful. If primary analysis of products is to be performed by gas chromatography, a chlorotrimethylsilane (ClTMS) derivative is preferable. Using this last method, the product yield can be easily calculated by comparing the corrected areas of product and starting material peaks.

D. Mechanistic Aspects

Substituents that withdraw electron density with no π-donation in an aryl system will act as meta- directors in EAS type reactions. Roberts and Curtin's experimentation with one of these EAS meta- directors, $-CF_3$, under DoM conditions produce metalation results that showed overwhelming ortho-substituted production. The conclusion was that the e-withdrawing capabilities of the substituent made the ortho-hydrogen more acidic

thereby facilitating its abstraction. In the same paper, Roberts and Curtin experimentally compared a strong e-withdrawing but non-coordinating substituent such as the trifluoromethyl group with the methoxy group which exhibits both coordination and e-withdrawal and found the methoxy group to be the stronger directing substituent. If the methoxy is not a stronger withdrawer than the trifluoromethyl group, why did the results show it to be more effective? Their explanation was that the alkyllithum reagent was becoming coordinated to the lone pairs on the methoxy group, thereby increasing the proximity of the lithium. This propinquity of reactants facilitated the lithium/ortho-hydrogen exchange (entropic effect). In addition, the coordinated intermediate furthered e-withdrawal from the aromatic ring. This withdrawal also served to enhance ortho-metalation by increasing the acidity of the ortho-hydrogen.

There are two general mechanisms that reflect the findings in the Roberts and Curtain paper. One of these mechanisms is that the ortho-proton is abstracted simply through acidity of that proton. As previously discussed, the acidity of that ortho proton is effected mainly by the electron withdrawing capability of the ring substituents and is the only effect operating for directing groups such as $-CF_3$. This so-called "overriding base"[27] mechanism, however, is separate from a second type of mechanism (Figure 3) that involves a prior-coordination complex between the alkyllithium and the DMG thereby constituting an important example of a pathway governed by a CIPE mechanism.

This second mechanism has two general steps. The preequilibrium step is formation of a coordination complex between the alkyllithium dimer and a lone pair on the DMG. These intermediates often form viscous and at times almost intractable complexes. Anisole would involve a coordination complex with the n-BuLi

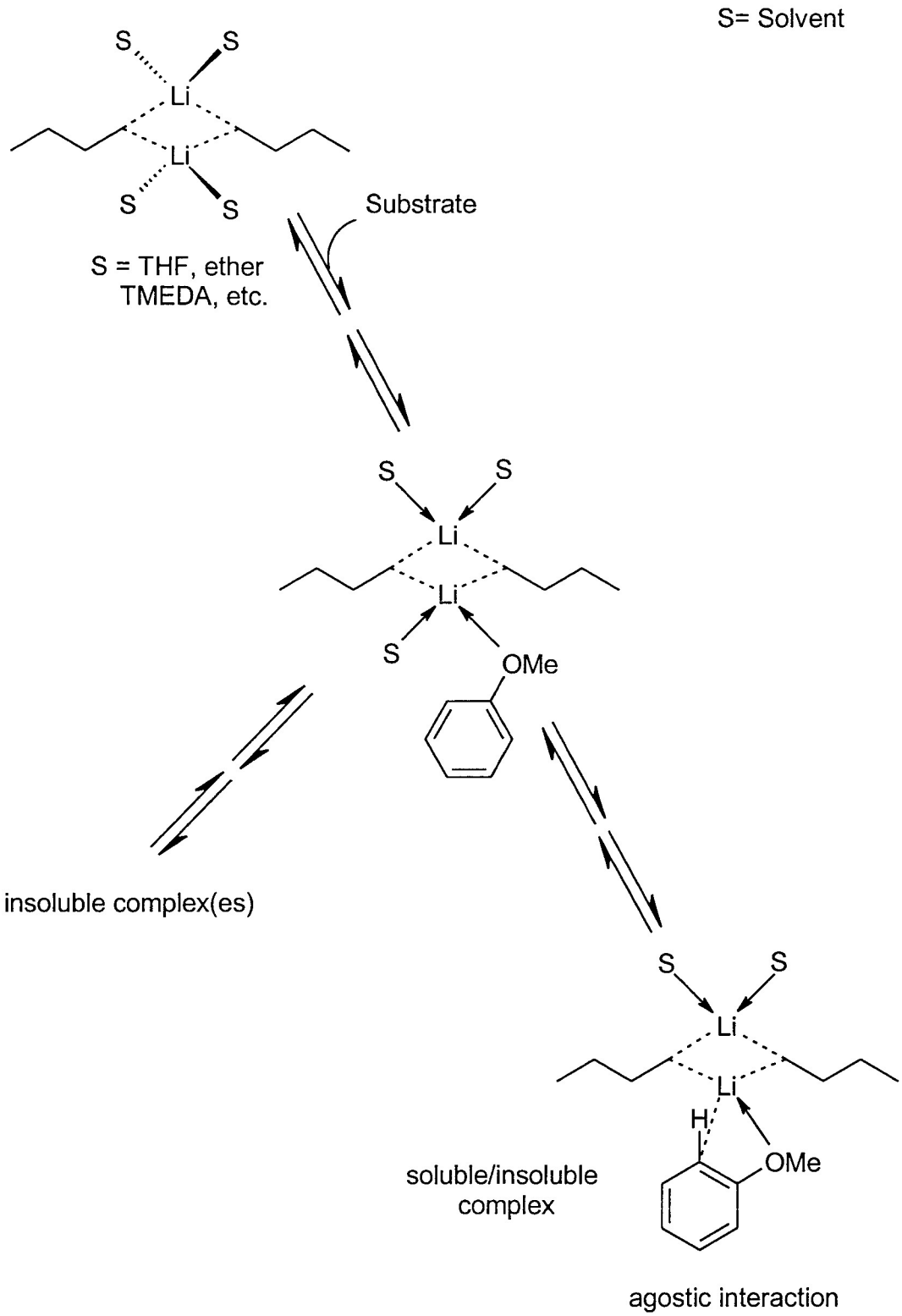


Figure 3. Dimer-substituent intereaction as part of overall CIPE contribution to overall DoM reaction.

dimer which develops a stoichiometry of n-$BuLi_2 \cdot A \cdot S_3$ where S is coordinating ether solvent and A is the anisole. In this instance anisole is coordinated from the oxygen atom to one of the lithiums in the dimer structure.

Secondly, by invoking the complex induced proximity effect[28], the lithium coordinated to the hetroatom will be attracted to the electrons in the ortho-hydrogen bond and will exchange positions with that hydrogen. In both mechanisms, the lithium-hydrogen exchange forms an ortho-lithio aryl intermediate.[29] Reactions where the DMG can both coordinate with the alkyllithium as well as withdraw e-density probably proceeds via a combination of both these mechanisms. Experiments to determine reaction rates have also been performed.[20,30] The results indicate that the rate-determining step is the abstraction of the ortho-proton, but no evidence for pre-equilibrium complexes has been found. Metalation studies on other substrates have provided some indications of pre-equilibrium complex formation.

As early as 1970, papers were published showing that TMEDA could be used as a catalyst for ortho-metalation.[21,22] Indications that the n-BuLi dimer stabilized by TMEDA is the important component in such metalation reactions have been accumulating since initially proposed in 1989 by Bauer and Schleyer.[29] A more recent demonstration, from our laboratories, of the necessity of generation of the inferred dimer intermediate involved ortho metalation of anisole "catalyzed" by THF in a hydrocarbon solvent.[31] The rate of metalation was, after 24 h, dramatically enhanced by the addition of THF (Figure 4). The inference was that THF, which supports the dimer structure, provided the dramatic acceleration of the rate of metalation.

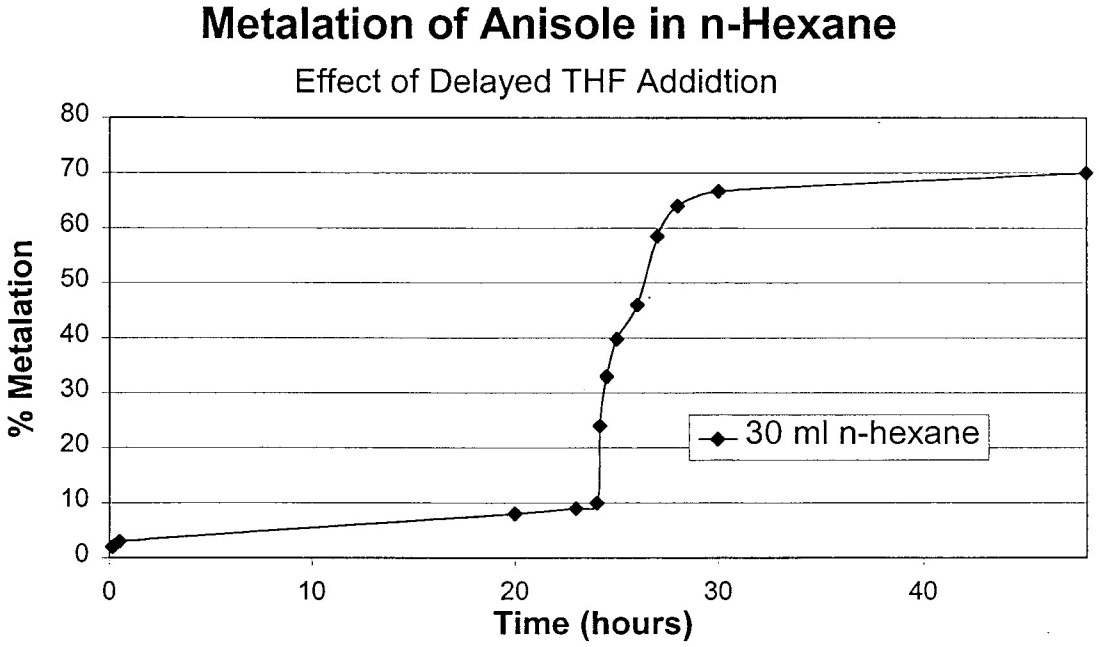


Figure 4. Effect of delayed THF addition.

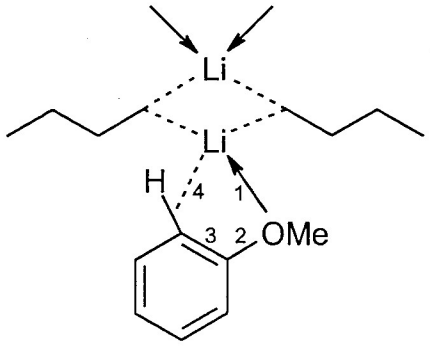


Figure 5. Formation of a four membered ring in anisole coordination of the n-BuLi dimer.

E. Directing Groups

Directing groups play an important role in the effectiveness of a DMG; certain characteristics will make some directing groups better than others. One example is coordinating ability of the DMG.[4] The better coordination ability the DMG possesses the more likely it is that the molecule will successfully undergo metalation. A second characteristic is the electron withdrawing capability of the DMG. If a highly electronegative group is attached to the ring, electron density is pulled away from the ortho-hydrogen making it more acidic. Another factor is the size of the ring formed in the transition state.[29,13] For example, when anisole reacts with n-BuLi a four-membered ring is formed (Figure 5). The four-membered ring size is not at all stable but will form temporarily as an agostic intermediate. This intermediate transforms through abstraction of the ortho-hydrogen to form the ortho-lithioanisole intermediate and butane.

Over time many different DMG's have been explored, and many were found to exhibit significant metalation capabilities. It is important that the researcher know which DMG's are stronger coordinators. Slocum and Jennings examined various directing groups and then experimentally ranked them in order from strongest to weakest (Figure 6).[32] There have also been other rankings of DMG's, most of which are compared to the methoxy group (Figure 7).[33,34,35]

Since some directors are stronger than others, an interesting situation occurs when two or more groups become involved. Little is known about the situation when two groups are ortho- to one another, but para-substituents will compete with each other in metalation. In fact, the stronger director is usually, but not always, the one that dictates

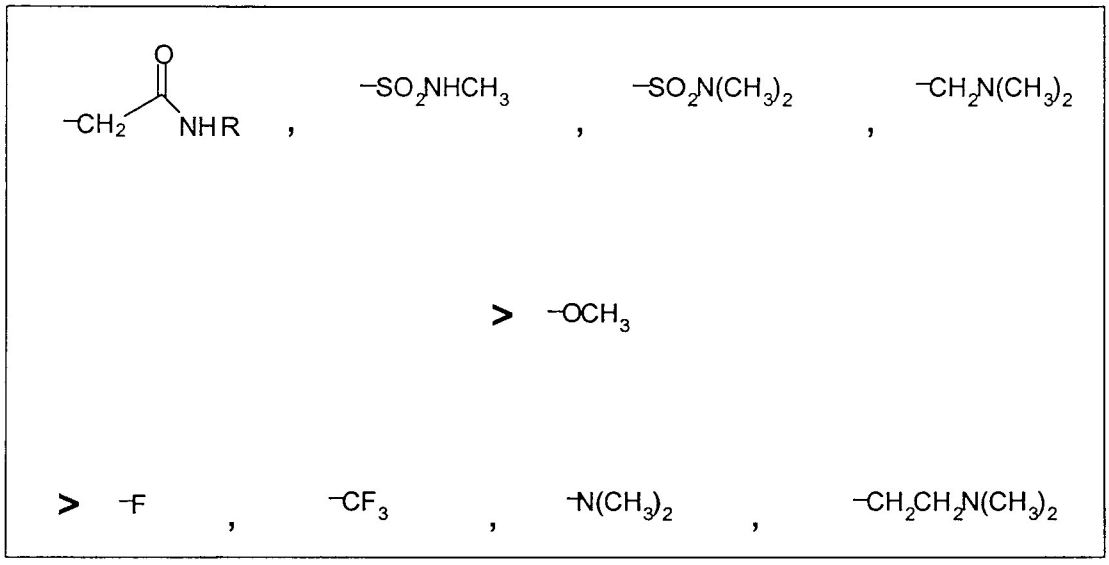


Figure 6. Activating groups as compared to the methoxy group.

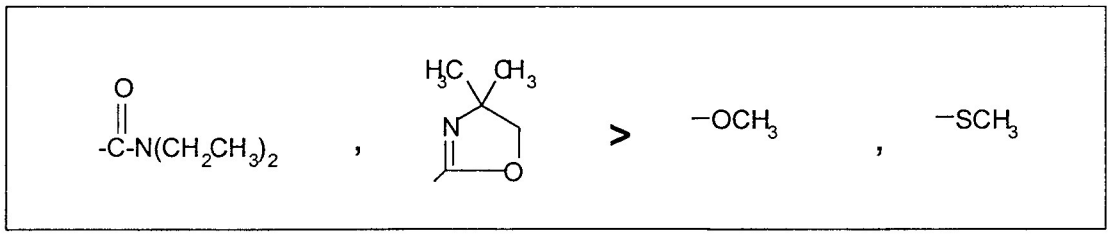


Figure 7. Activating groups as compared to the methoxy group.

metalation.[32,36,37] When two directing groups are meta to each other a different situation exists. Early research suggested that under these conditions insertion between the two groups was remarkably favored. This outcome is due to the fact that both directors will guide metalation to the same position. This pattern of substitution being most difficult under EAS conditions provides a unique aspect of the DoM methodology. Saa details an interaction in which two DMG's are meta to one another on the aromatic ring.[38] In the example shown (Figure 8), the two DMG's each coordinate to one of the lithiums. Saa

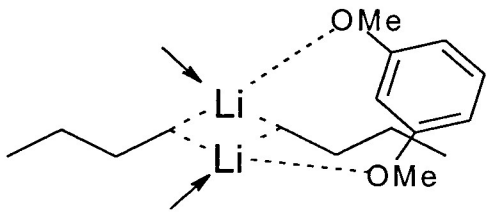


Figure 8. Bis-coordination of 1,3-DMB.

called this interaction the tweezer effect and computed such structures to be at an energy minimum.

Aside from competition, another effect will be evidenced whenever both p-substitutents have lone electron pairs. The rate of metalation is expected to increase due to an effect known as opposing π-resonance.[39] The opposing π-resonance effect results in increased localization of the coordinating lone pairs on the two substituents. During e-donation to the ring, canonical forms which localize a negative charge at each ortho-postion and at the p- position will be generated (Figure 9). The electron rich para-substituent will deter the placement of electron density at the p- carbon due to electronic repulsion. Therefore, the electron density on the methoxy group in the example shown is higher than that in anisole itself. It is less delocalized. Such a contribution by the p-Cl

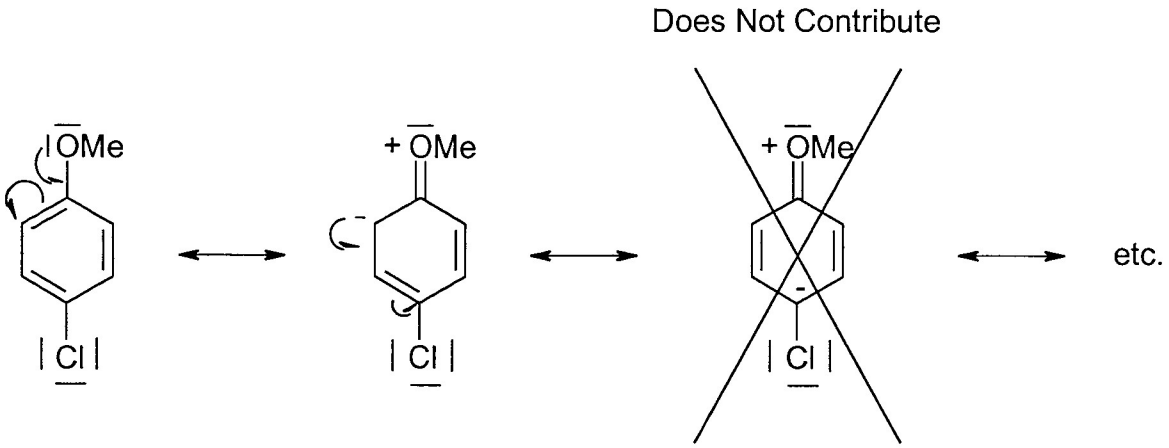


Figure 9. Opposing π resonance.

group predicts that p-ClA in comparison to anisole should more readily form the preequilibrium complex. This prediction has been observed.[48]

An alternative interpretation of acceleration provided by an e-withdrawing group is that inductive e-withdrawal acidifies the C-H bond adjacent to the coordinating DMG. This acidification would also provide a more rapid rate of metalation. It is also possible that both effects can contribute to the observed acceleration.

F. Metalation of Various Substrates

In order to fully understand the metalations of di- and tri-methoxybenzenes, knowing their history is useful. A survey of some of the most heavily researched methoxybenzenes needs to be undertaken starting with the simplest, anisole. From there a synopsis of past research involving alkylanisoles, haloanisoles and multi-methoxyanisoles will be undertaken.

1. Metalation of Anisole

The earliest metalation research was that of Gilman and Wittig.[6] At 25 °C using n-BuLi in ether solvent, Gilman was able to attain ortho-metalated anisole as a major

product. Wittig, on the other hand, used harsher conditions by refluxing the reaction in ether with a weaker metalating reagent, but the same result was found. This data was supported in 1968 when Shirley *et. al* repeated the reaction with anisole.[40] They also reported metalation at only the ortho- position. Finnigan and Altshuld attempted metalation of anisole in tetrahydrofuran and reported a 49-51% yield.[41] This product, however, was trapped by carbonation with dry ice--a method where loss of solid product is potentially high. This reaction was also reproduced by Shirley and Hendrix.[40] They reported a carbonation percentage very similar to that of Finnigan and Altshuld (41-55%).

When researchers began quenching reactions in chlorotrimethylsilane, the advantages over carbonation became evident. According to Crowther *et. al*, a 72% yield can be obtained by quenching o-Li anisole with chlorotrimethylsilane.[42] Crowther's experiments were carried out with addition of 3.1 equivalents of both TMEDA catalyst and n-BuLi at room temperature. The reaction took 12 hours to achieve maximum yield in ether solvent. Slocum *et al.* found that further improvements can be made through addition of incremental TMEDA leading to production of greater than 95% after two hours with 2 eq. n-BuLi and ether solvent.[39]

2. Metalation of Alkylmethoxybenzenes

In the early 1950's, Letsinger and Schnizer examined the use of sodium and n-BuLi to metalate alkylmethoxybenzenes.[43] They determined the products of metalation of 2- and 4-methylanisole. In both these systems, excess substrate was added to an equivalent amount of n-BuLi. For 2-methylanisole, 12.9% yield of the 6-carboxylic acid derivative through carbonation was isolated and significant lateral metalation was also

detected. This paper reported a slightly higher 31.5% yield of the 2-carboxylic acid derivative in the 4-methylanisole metalation. 2-Ethylanisole was also examined and found to give a better yield (33%) of the 6-carboxylic acid product analogous to that found for methylanisole. Where 2-methylanisole displayed lateral metalation, however, no lateral metalation was detected in the 2-ethylanisole reaction.

Until 1995 metalations utilizing addition of TMEDA catalyst were carried out with full or excess equivalents of TMEDA. At this point a paper was published working with 4-methylanisole showing that by using incremental amounts (0.2–0.5 equivalents) of TMEDA, extents of metalation could be drastically improved.[39]

Shirley, Johnson and Hendrix pioneered work with the 3-methyl anisole substrate.[44] They discovered that maximum yield could be obtained in approximately 3.5-4 hours. A mixture of the 2- and 6-carboxylic acid products was formed. The 2-product was found to yield a maximum of 21.2% as opposed to 31.8% for the 6-product. Products from lateral metalation and demethylation were also found in minute amounts. By 1974 Shirley published a more extensive paper on 3-methylanisole.[45] Here various solvents and alkyllithiums were investigated. Percent yields were not reported, because emphasis was placed on the ratio of 2 to 6-substitiution. With n-BuLi in ether, this paper showed 59-61% of the total product at the 6 position and 39-41% of the product at the 2 position. When n-BuLi was examined in cyclohexane 90-91% of the product obtained was metalated in the 6-position with the 2-position comprising the remaining 9-10%. By replacing n-BuLi with *t*-BuLi in cyclohexane, a lower ratio (70% : 30%) was obtained for metalation at the 6- and 2-positions. Lastly, by using TMEDA with n-BuLi, the 6- and 2-positions were metalated to the extents of 51-53% and 47-49%, respectively.

One paper has addressed the question of steric hindrance to formation of the n-BuLi-coordinated intermediate in alkylmethoxybenzenes. Slocum and Koonsvitsky experimented with such a compound by adding a bulky *t*-butyl substituent ortho- to the methoxy group.[25] Metalation of this compound produced an average 7.5% yield. This yield is considerably less than that reported in earlier papers for anisole. The conclusion was evident that addition of more bulky groups will increase steric hindrance and decrease product formation. Shirley and Harmon argued against this conclusion saying the anisole has twice as many ortho-hydrogens to exchange. Therefore, anisole should afford a higher yield based on a statistical perspective. They originally argued that this evidence did not necessarily prove there was any steric hindrance involved; however, they later retracted that view.[45] In a different paper it was shown that by changing the methoxy group first to an ethoxy and then to an isopropoxy group the formation of the ortho product progressively went down.[41] These results prove that increasing the size of the alkyl group on the ether will hinder coordination to the BuLi oligomer thereby lowering the yield.

In methoxyanisole experiments the Bates rearrangement can take place.[46] When reactions are run with superbase (RLi · KOtBu), a lateral methyl group can become substituted with a methyl group. This group comes from the methoxy substituent through an unexpected demethylation which leaves a negative charge on that oxygen (Figure 10). This rearrangement is not very common but will occur best with 2-methylanisole. 3-Methylanisole is less likely to undergo this rearrangement than is 2-methylanisole but more likely to rearrange than 4-methylanisole.

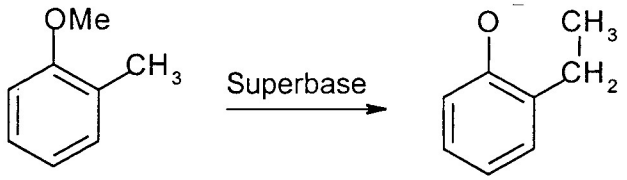


Figure 10. Bates rearrangement of 2-methylanisole.

3. Metalation of Haloanisoles

When trying to metalate a haloanisole it is important to realize that there are some side reactions that will take place under specific metalation conditions. Fluoro- and chlorobenzene can undergo ortho-metalation/elimination resulting in formation of a triple bond on the aromatic ring, benzyne formation (Figure 11).[32,37,47] Though previously

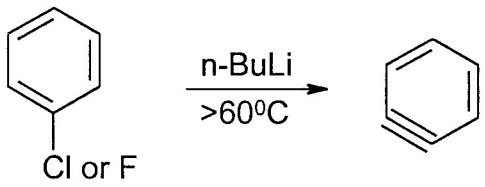


Figure 11. Benzyne formation of fluoro- or chlorobenzene.

thought not to readily form benzyne, a recent paper shows that chloroanisole can also undergo this process.[48] Furthermore, at higher temperatures benzyne formation is increased to the point of its being the major product. Bromine and iodine containing molecules do not undergo benzyne formation, but will quickly undergo a different side reaction known as halogen-metal exchange. The halogen metal exchange will replace the halogen on the aromatic with a lithium atom from the alkyllithium reagent.[32]

The initial work done with the haloanisoles was perfomed by Gilman, Langham and Moore[49] and Langham, Gilman and Brewster.[50] For the para-haloanisoles, the results of the metalation and carbonation of the bromo- and chloro- starting materials were almost identical (≅ 21.5%). The fluoro-substrate afforded slightly less product with

17.7% yield being reported. These reactions were carried out with methyllithium and run for 14 hours in ether at 34°C. n-BuLi[51] and phenyllithium[52,53] were also utilized by these researchers with comparable results.

In a later paper, 4-fluoroanisole was investigated further by Slocum and Jennings.[32] Through experimentation with ether and hexane as solvents and by varying temperatures (-50°C to 25°C), conditions were found permitting a maximum yield (32%) of the 2-carboxylic acid. To get this product, they tried both THF and TMEDA but found THF to be more advantageous for this particular process. Not only did they look at 4-fluoroanisole but also examined 2-fluoroanisole.[32] Upon analysis of the 25°C runs it was determined that no metalation had occurred, possibly due to simultaneous coordination of the fluorine and methoxy groups. Some evidence of demethylation was observed. Data reported by Furlano *et al.* conflicted with this conclusion for 2-fluoroanisole.[54] In ten minutes at -78 °C a quench with DMF was found to afford 64% in total product when using sec-BuLi. Within this 64% the overwhelming majority of it was the product ortho- to the methoxy, but a small amount was shown to metalate ortho- to the fluoro. Furlano also examined metalation of 4-fluoroanisole in the same paper. His group found that under the same conditions utilized in the 2-fluoroanisole reactions, a total yield of 75% was produced within 5 minutes. In this case the 2-position was substituted three times more than the 3-position.

Cited in the literature were two methods to predominantly metalate 2-fluoroanisole and 3-fluoroanisole adjacent to the fluoro-group rather than the methoxy group. One way is by using an n-BuLi/pentamethyldiethylenetriamine (PMDTA) complex at low temperatures.[37] The second method is through use of a

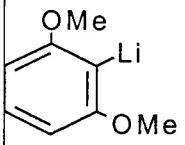
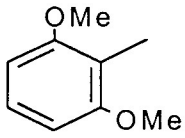
(tricarbonyl)chromium(0) reagent to complex the 4-fluoroanisole starting material. In this case metalation at the 3-position is effected in very high regiospecificity.[55]

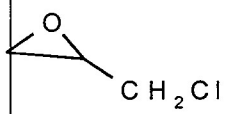
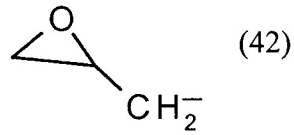
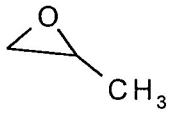
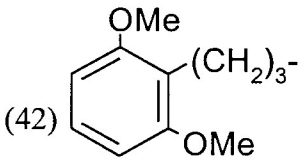
4. Metalation of the Di- and Trimethoxybenzenes

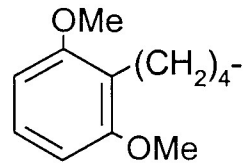
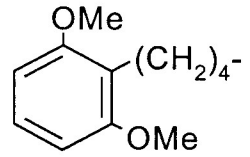
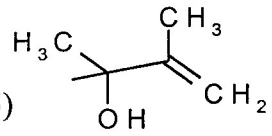
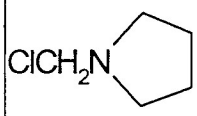
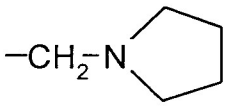
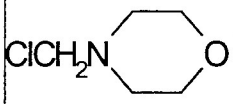
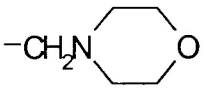
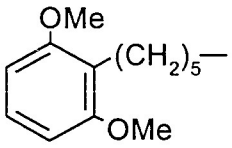
Dimethoxybenzenes (DMB's) and trimethoxybenzenes (TMB's) are used extensively throughout the literature in metalation syntheses. For instance, one impressive paper by Kumar and Manickam links three 1,2-dimethoxybenzene (veratrole) molecules by oxidative coupling in order to form a hexalkyltriphenylene.[56] In order to provide some indication of just how important the metalation of di- and trimethoxybenzenes is, a listing of all such references has been complied (Table 1 – 6). This list is not exhaustive but is informative through inclusion of sections on the compound metalated, conditions used and percent yield achieved.

The literature has focused mainly on monometalation of the DMB's and TMB's; each system was examined under a variety of conditions and with use of numerous quenching agents. One important point of note is that, in almost every case, ether solvents were used. In fact, for metalation of 1,3-DMB about fifty entries appeared in Gschwend and Rodriguez[12] and, in all of these, some type of ether solvent was used. 1,3-DMB is by far the most often metalated multimethoxybenzene (Table 1), likely attributable to the high reactivity reported for this substrate. For instance, one paper reported a 90% yield when quenching with $BrAuP(C_6H_5)_3$ in order to add a gold substituent to the ring.[12] Yet another researcher was able to substitute 1,3-TMB with an allylic carbon chain in 98% yield. This process, however, did take up to 2-3 days in ether

Table 1. Metalation of m-DMB.

Reference Number	Lithiated Compound	Conditions	Reactant	Product at Site of Li And Yield (%)
12		C_6H_5Li/ Ether/ 2-3 days	Cl_2	– Cl (39)
12		C_6H_5Li/ Ether/ 60 hr	Cu	 (48)
12		BuLi/ Ether/ 25°/70 hr	CuBr	– Cu (93)
12		C_6H_5Li/ Ether/ 2-3 days	Br_2	– Br (18)
12		BuLi/ Ether	AgBr	– Ag (21)
12		C_6H_5Li/ Ether/ 2-3 days	I_2	– I (80)
12		BuLi/Ether 25°/70 hr	$(CH_3)_2SnBr_2$	– $Sn(CH_3)_2Br$ (87)
12		C_6H_5Li	$B(OCH_3)_3$	– $B(OH)_2$ (48)
12		BuLi	$(CH_3)_3SnCl$	– $Sn(CH_3)_3$
12		-	$BrAuP(C_6H_5)_3$	– $AuP(C_6H_5)_3$ (90)
12		BuLi/ Ether/ Reflux/ 2 hr	CO_2	– CO_2H
12		C_6H_5Li/ Ether/ 2-3 days	BrCN	– Br (46)
12		"	ICN	– I (46)
12		C_6H_5Li/ Ether/ 25°/60 hr	CH_3I	– CH_3 (95)

12		C_6H_5Li/ Ether/ 2-3 days	$(SCN)_2$	– CN (6) – SCN (21)
12		"	AcCl	– Ac (14)
12		"	Ethylene Oxide	– $(CH_2)_2OH$ (57)
12		"	$Br(CH_2)_2Br$	– Br (71)
12		"	$ClCH_2OCH_3$	– CH_2OCH_3 (62)
12		"	C_2H_5I	– C_2H_5 (6)
12		C_6H_5Li/ 25°/ 3 days	$(CH_3O)_2SO_2$	– CH_3 (74-76)
12		C_6H_5Li/ Ether/ 2-3 days	$BrCH_2CH=CH_2$	– $CH_2CH=CH_2$
12		"		 (42) – $CH_2CH(OH)CH_2Cl$ (18)
12		BuLi/ THF/ Reflux/ 1hr		– $CH_2CH(OH)CH_3$ (28)
12		C_6H_5Li/ Ether/ 2-3 days	CH_3COCH_3	– $C(CH_3)_2OH$ (61)
12		C_6H_5Li/ Ether/ 60 hr	$1/2Br(CH_2)_3Br$	 (42)
12		C_6H_5Li/ Ether/ 25°/ 2days	$ClCH_2N(CH_3)_2$	– $CH_2N(CH_3)_2$ (33)
12		C_6H_5Li/ Ether/ 2-3 days	$BrCH_2CH=CHCH_3$	– $CH_2CH=CHCH_3$ (75)
12		"	$(CH_3)_2CHCHO$	– $CH(OH)CH(CH_3)_2$ (76)

12		C_6H_5Li/ Ether/ 60 hr	$1/2Cl(CH_2)_4Br$	(33) 
12		"	$1/2Br(CH_2)_4Br$	(63) 
12		"	$Cl(CH_2)_4Br$	– $(CH_2)_4Cl$ (45)
12		"	$Br(CH_2)_4Br$	– $(CH_2)_4Br$ (45)
12		C_6H_5Li/ Ether/ 2-3 days	$(C_2H_5O)_2SO_2$	– C_2H_5 (18)
12		"	$CH_2=C(CH_3)COCH_3$	(35) 
12		"	$BrCH_2CH=C(CH_3)_2$	– $CH_2CH=C(CH_3)_2$ (98)
12		C_6H_5Li/ Ether/ 25° 2 days		 (55)
12		"		 (55)
12		C_6H_5Li/ Ether/ 60 hr	$1/2Br(CH_2)_5Br$	(58) 
12		C_6H_5Li/ Ether/ 25° 2 days	$ClCH_2N(C_2H_5)_2$	– $CH_2N(C_2H_5)_2$ (68)

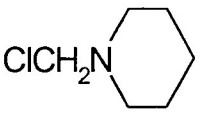
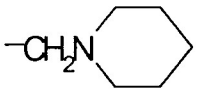
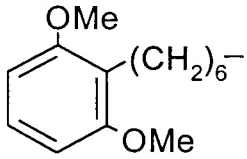
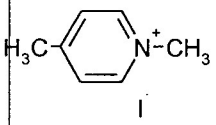
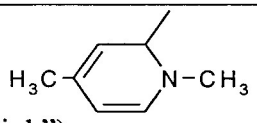
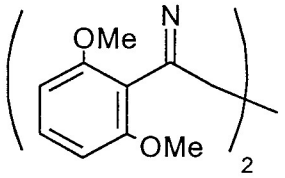
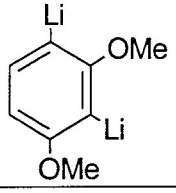
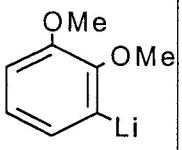
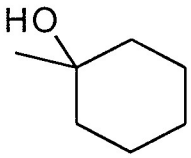
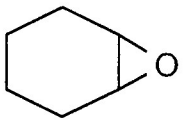
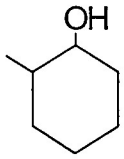
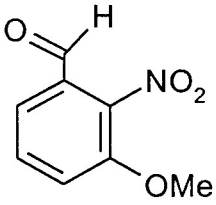
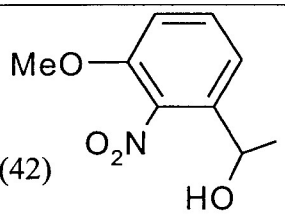
12		C_6H_5Li/ Ether/ 2-3 days	$(CH_3)_2C{=}CHCOCH_3$	$HOC(CH_3)CH{=}C(CH_3)_2$ (59)
12		"	$CH_3COC_4H_9$-*t*	$HOC(CH_3)C_4H_9$-*t* (29)
12		C_6H_5Li/ Ether/ 25° 2 days		 (49)
12		C_6H_5Li/ Ether/ 60 hr	$1/2Br(CH_2)_6Br$	 (64)
12		BuLi/ Ether/ -5°		 ("high")
12		C_6H_5Li/ Ether/ 2-3 days	$C_6H_5CH{=}CHCHO$	$-CH(OH)CH{=}CHC_6H_5$ (79)
12		BuLi/THF/ -20°/2 hr	n-$C_{12}H_{25}Br$	$-C_{12}H_{25}$-*n* (70)
12		C_6H_5Li/ Ether/ 2-3 days	$(CN)_2$	(54) 
42		1.1 eq. BuLi/ Ether/ TMEDA 25°/26 hr	ClTMS	– TMS (83)
42		5.0 eq. BuLi/ Ether/ TMEDA/ Reflux /36 hr	ClTMS	– TMS (72)
42		2.1 BuLi/ Ether/ TMEDA/ 25°/11 hr	ClTMS	– TMS (>95) bis-TMS (<2)

Table 2. Metalation of o-DMB.

Reference Number	Lithiated Compound	Conditions	Substrate	Product at Site of Li and Yield (%)
12		C_6H_5Li	$B(OCH_3)_3$	– $B(OH)_2$ (20)
12		BuLi/ Ether/ 25°/24 hr	Cyclohexanone	 (60)
12		"		 (70)
57		0.6667 eq. BuLi/ THF/ 0°/2hr	Br-$C_{10}H_{21}$	– $C_{10}H_{21}$ (73)
58		1.06 eq. BuLi/ Ether/ TMEDA/ 25°/4 hr		 (42)
59		0.9 eq. BuLi/ THF/ 0°/2 hr	$B(OCH_3)_3$	– $B(OH)_2$ (60)
60		BuLi/ Ether/ TMEDA/ 0°	$B(OCH_3)_3$	– $B(OH)_2$ (92)
61		1 eq. BuLi/ Ether/ TMEDA/ 25°/1 hr	Br_2	– Br (81)

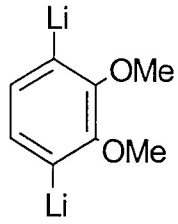
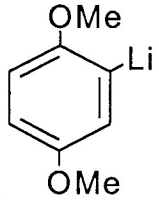
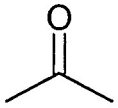
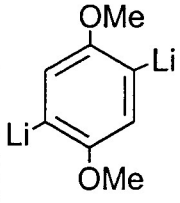
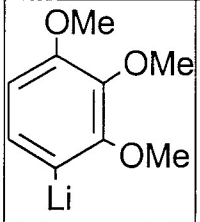
42		1.1 Eq. BuLi/ Ether/ TMEDA/ 25°/46 h	ClTMS	– TMS (86)
12		BuLi/ Heptane/ TMEDA/ 25°/24 hr	I_2	– I (2)
42		5.0 Eq. BuLi/ Ether/ TMEDA/ Reflux/ 10 h	ClTMS	– TMS (10) bis-TMS (87)

Table 3. Metalation of p-DMB.

Reference Number	Lithiated Compound	Conditions	Substrate	Product at Site of Li and Yield (%)
62		BuLi/THF		– $C(CH_3)_2OH$ (81)
62		BuLi/THF/ 25°/1hr	MeI	– Me (Nearly Quantatative)
42		1.1 eq. BuLi/ Hexanes/ 25°/71 hr	ClTMS	– TMS (75)
42		5.0 eq. BuLi/ Ether/ TMEDA/ reflux/ 24 hr	ClTMS	– TMS (10) bis-TMS (90)

42		4.0 eq. BuLi/ Ether/ TMEDA/ 25°/71 hr	ClTMS	– TMS (12) bis-TMS (88)
42		3.0 eq. BuLi/ Hexanes/ TMEDA/ 25°/91 hr	ClTMS	– TMS (5) bis-TMS (94)

Table 4. Metalation of 1,2,3-TMB.

Reference Number	Lithiated Compound	Conditions	Substrate	Product at Site of Li and Yield (%) NY = No Yield Reported
12		BuLi/THF/ 25°/2 hr	D_2O	– D (94)
12		BuLi	CO_2	– CO_2H (40)
12		BuLi/THF/ 25°/2 hr	C_2H_5Br	– C_2H_5 (56)
12		"	*n*-$C_{12}H_{25}Br$	– $C_{12}H_{25}$-*n* (NY)
63		1 eq. C_6H_5Li/ Ether/ 25°/2 hr	D_2O	– D (<10)
63		1 eq. C_6H_5Li/ THF/ 25°/2 hr	D_2O	– D (21)
63		1.1 eq. BuLi/ THF/ -15°/2 hr	D_2O	– D (19)
63		1.1 eq. BuLi/ THF/ 0°/2 hr	D_2O	– D (54)

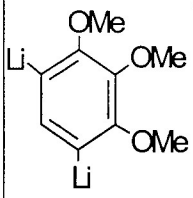
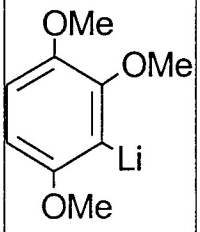
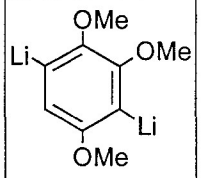
63		1.1 eq. BuLi/ THF/ 25°/2 hr	D_2O	– D (75)
63		2.2 eq. BuLi/ THF/ 25°/2 hr	D_2O	– D (94)
42		1.1 eq. BuLi/ Ether/ TMEDA/ 25°/27 hr	ClTMS	– TMS (84)
42		2.2 eq. BuLi/ Hexanes/ Ether/ TMEDA/ 25°/76 hr	ClTMS	– TMS (49) bis-TMS (8)

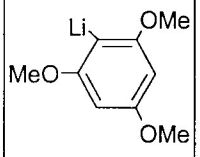
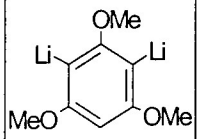
Table 5. Metalation of 1,2,4-TMB.

Reference Number	Lithiated Compound	Conditions	Substrate	Product at Site of Li and Yield (%) NY = No Yield Reported
62		1.1 eq. BuLi/ THF	1. EtO_2CCl 2. MeMgBr	– $C(CH_3)_2OH$ (80)
62		1.1 eq. BuLi/ THF/ 25°/1 hr	MeI	– Me (95)
62		1.1 eq. BuLi/ THF/ 25°	ClTMS	– TMS (80)
64		1.0 eq. BuLi/ Ether/ TMEDA	$(PrS)_2$	– SPr (NY)*

64		1.0 eq. BuLi/ Ether/ TMEDA	ClTMS	– TMS (NY)*
42		1.1 eq. BuLi/ Hexanes/ TMEDA/ 25°/16 hr	ClTMS	– TMS (80)
64		2-6 eq. BuLi/ Ether/ TMEDA	2-6 eq. ClTMS	– TMS (58)
64		2-6 eq. BuLi/ Ether/ TMEDA	2-6 eq. $(PrS)_2$	– TMS (NY) *
42		3.0 eq. BuLi/ Ether/ TMEDA/ 0°/24 hr	ClTMS	– TMS (46) bis-TMS (55)
42		3.0 eq. BuLi/ Hexanes/ TMEDA/ 25°/ 67.5 hr	ClTMS	– TMS (31) bis-TMS (49)
42		3.0 eq. BuLi/ Ether/ TMEDA/ 0°/8 hr	ClTMS	– TMS (52) bis-TMS (48)
42		3.0 eq. BuLi/ Hexanes/ TMEDA/ 25°/96 hr	ClTMS	– TMS (26) bis-TMS (42)

* This is the first step of a larger one pot synthesis so no yield is recorded.

Table 6. Metalation of 1,3,5-TMB.

Reference Number	Lithiated Compound	Conditions	Substrate	Product at Site of Li and Yield (%)
12		BuLi/ether/ 25°/70 hr	CuBr	– Cu (65)
12		BuLi/ether	AgBr	– Ag (21)
12		BuLi/ether/ 25°/70 hr	$(CH_3)_2SnBr_2$	– $Sn(CH_3)_2Br$ (95)
12		BuLi/THF	$(CH_3)_2SnCl$	– $Sn(CH_3)_3$
12		----	$BrAuP(C_6H_5)_3$	– $AuP(C_6H_5)_3$ (60)
64		2.0 eq. BuLi/ Ether/ TMEDA	$(PrS)_2$	– PrS *
64		2.0 eq. BuLi/ Ether/ TMEDA	ClTMS	– TMS*
42		1.1 eq. BuLi/ Ether/ TMEDA/ 25°/26 hr	ClTMS	– TMS (76)
64		2-7 eq. BuLi/ Ether/ TMEDA	2-6 eq. $(PrS)_2$	– PrS *
64		2-6 eq. BuLi/ Ether/ TMEDA	2-6 eq. ClTMS	– TMS (86)
42		3.0 eq. BuLi/ Hexanes/ TMEDA/ 25°/71 hr	ClTMS	– TMS (14) bis-TMS (86)
42		3.0 eq. BuLi/ Ether/ TMEDA/ 25°/11 hr	ClTMS	– TMS (14) bis-TMS (86)

* This is the first step of a larger one pot synthesis so no yield is recorded.

solvent using the weaker reagent, PhLi.[12] Another interesting reaction occurred wherein a long C_{25} chain was placed on the aromatic substrate in a 70% yield.[65]

Where about fifty reactions were reported in the review by Gschwend and Rodriguez for 1,3-DMB, only four entries appeared for 1,2-DMB (common name: veratrole dimethyl ether), but, since that review, there has been increased interest in this compound. In 1978, Ng and Dawson, using a deficiency of n-BuLi (.67 eq.), were able to add a ten carbon chain onto the aromatic ring in 73% yield by trapping with $BrC_{10}H_{21}$.[57] Intricate molecular additions can also be carried out as shown in a paper by Albrecht *et al.*[59] In this reaction an aromatic trapping agent was used in order to form a bis-aromatic compound. An n-BuLi/TMEDA system was used in ether solvent in order to produce 42% of the biphenyl within 4 hours. One example of how dependent metalations are on the conditions comes from the comparison of two 1,2-DMB metalations where both are quenched with $B(OCH_3)_3$. Both papers reported use of n-BuLi at 0°C, but one used a TMEDA/Ether system[60] while the other used neat THF.[59] The yield disparity here is great: one system will yield 60% and the other a much higher 92% yield. Again, note that only ether media were used in all the reactions reported for 1,2-DMB (Table 2). Discussion and investigation of 1,4-DMB is not included in this thesis due to this molecule's inability to bis-coordinate n-BuLi. No reactions are reported in the Gschwend and Rodriguez review; however, a few have been reported in the recent past.[42,62]

1,2,3-TMB has also been looked at by various researchers examining the DoM reaction (Table 3). One paper reported 94% yield of the deuteriated derivative when 1,2,3-TMB is quenched with D_2O.[12] All reactions with this substrate do not go so readily though as is seen in a paper by Mathison *et al.*[66] In this paper a carbonation product was

formed to an extent of only 40%. Schill has done research pertaining to 1,2,3-TMB under various conditions.[63] By varying the alkyllithium reagent, solvent and temperature, Schill was able to get a deuterium incorporation of 1,2,3-TMB, ranging from <10% yield to 94% yield.

Monosubstitution of 1,2,4-TMB (Table 4) and 1,3,5-TMB (Table 5) has not been attempted often in the literature. However, in a paper by Carreno *et al.* 1,2,4-TMB was quenched with EtO_2CCl (80% yield), MeI (95% yield) and ClTMS (80% yield).[62] Each of these reactions was run in THF containing 1.1 eq. n-BuLi. The best yield for monometalation of 1,3,5-TMB was done by Van Koten *et al.* in 1972.[67] He reported 95% yield of a tin derivative after 70 hours in ether. Most of the recent papers on directed ortho-metalations of 1,2,4- and 1,3,5-TMB have been on the dimetalation of these substrates.

Of all the papers investigating dimetalation, that by Sundberg *et al.* in 1984 is by far the most definitive publication on metalation of the di- and trimethoxybenzenes to date.[42] More specifically, the researchers examined all six compounds under various conditions. According to this paper there have been a small number of attempts at monometalation in the literature but only two where the dimetalated species was formed. One of these reactions dimetalated separate aromatic rings.[68] The other paper reported attempts to dimetalate veratrole in diethyl ether by quenching with iodine.[69] These reactions were carried out at 25°C with 2.5 equivalents of an equimolar n-BuLi/TMEDA solution. The two ortho- positions were metalated, but this time even though excess BuLi was present only 2% of the diiodinated product was isolated.

Sundberg *et al.*, wanting to improve upon past attempts at dimetalation, looked at all the di- and trimethoxybenzenes.[42] 2.2 or more equivalents of n-BuLi with equal equivalents of TMEDA were added to the substrate in either an ether or hydrocarbon solvent. Some problems were encountered with formation of a thick precipitate, long reaction times, and the necessity of elevated temperatures to gain significant amounts of metalation. Most of these runs were quenched with ClTMS, though at times it was necessary to trap with D_2O for NMR studies or carbon dioxide for crystallography studies.

Sundberg tried two pathways to maximize dimetalation for each of the methoxybenzenes. In the first, a stepwise approach was taken where the monometalated species was formed and then additional n-BuLi was injected into the system effecting a second metalation. The second method involved a one step synthesis where up to five equivalents of n-BuLi was added to produce relatively high yields of the di-metalated species. When the stepwise approach was taken with 1,2-DMB, the researchers were able to obtain a mono-metalated product in 70-86% yield. The second addition of BuLi showed 73% of the bis-TMS derivative. The alternative one step approach found that the bis-product could be obtained in 50-60% with 10% contamination of the mono-product. The best conditions for this reaction were found to be at reflux for 10-12 hours. Ether was again used as a solvent with five equivalents of n-BuLi/TMEDA.

For the two step approach to 1,3-DMB an 83% TMS yield was obtained for the first step with a smaller 47% yield of the 2,6-bis-TMS product after the second metalation step. 1,3-DMB, unlike 1,2-DMB, would not undergo the one step reaction. Even when the excessive amount of five equivalents of n-BuLi was used, there was no

bis-product reported, and only 72% of the singly substituted aromatic was found. These results agree with other researchers who reported highly selective yields of 1,3-DMB derivatization at the 2-position.[25,40] The final DMB, 1,4-DMB, afforded 75% and 18% of the mono- and di-substituted products, respectively, when performing the two step process. When the one step process was utilized, 8-9 times more bis-TMS product was found as compared to the mono-TMS product where 68% of the total yield was the bis-TMS product.

Metalation of 1,2,3-TMB was also performed by Sundberg *et al.*[42] Since, in hexane solvents, this substrate was found to be unreactive the experiment was carried out in ether. In the two step process the first metalation/derivatization sequence yielded 84% of the mono-product, and the second step produced the bis-TMS product in 68% overall yield as determined by VPC analysis. Alternatively, when the one step reaction was run a low 20% yield of the 4,6-TMS product was obtained. A second trimethoxybenzene, 1,2,4-TMB, was run in the two step fashion leading to production of 80% mono-TMS product in the first step and a yield of 82% of the 3,6-TMS product in the second step. Again VPC analysis showed that when attempts to di-metalate this species in one step were performed, a 55% yield of the 3,6-TMS product was obtained.

The only other compound examined by Sundberg, 1,3,5-TMB, afforded 76% of the monometalated intermediate with significant yields of the bis-product being formed when a second metalation was utilized. These yields, however, were overshadowed by an 85-95% production of the bis-TMS-product with the one step method. Though a high percentage of metalation was found, three equivalents of a n-BuLi/TMEDA complex was necessary and the reaction required 71 hours. In conclusion to this study, Sundberg *et al.*

summarized the results by ranking the ease with which the di- and trimethoxybenzenes undergo dimetalation. They concluded that 1,4-DMB and 1,3,5-TMB undergo dimetalation with slightly higher facility than 1,2-DMB. All three of these compounds, however, undergo dimetalation significantly better than 1,2,4-DMB and 1,2,3-DMB. Finally, anisole and 1,3-DMB are shown to undergo no one-step dimetalation. Sundberg's proposed reason for this outcome is the fact that once the lithium atom is substituted onto the ring, the ortho methoxy groups are coordinated to that lithium, thereby making them unavailable to further coordinate to free n-BuLi hindering the addition of a second substituent.

Although Sundberg *et al.* extensively examined the dimetalation scheme they are not the only ones to probe into the mechanics behind this process. Cabbidu *et al.* not only examined dimetalation but also took this concept one step farther to test if it was possible to trimetalate an arene substrate.[64] The remarkable finding in this paper is that Cabbidu *et al.* trisubstituted 1,2,4- and 1,3,5-TMB leading to the production of hexasubstituted benzenes. They attempted trimetalation by adding excessive amounts (six equivalents) of n-BuLi to the TMB but found a trilithio intermediate was not produced in one step. Findings revealed however that it was possible to metalate in three different ways. The first is to dimetalate the aromatic followed by a monometalation step. Secondly, a monometalation could be carried out followed by a dimetalation step. Finally, three subsequent monometalatons could be done. As might be expected, steric hindrance became problematic from steric hindrance in both the 1,2,4- and 1,3,5-TMB substrates when a trimetalation was attempted. In either case a disubstitution could be achieved with bulky TMS groups, but a third TMS group could not be added to the

aromatic ring. However, after two TMS groups were substituted a third, smaller substituent, deuterium, could be successfully placed on the remaining ring position by quenching with D_2O. It was also possible to quench both the 1,2,4- and 1,3,5-TMB substrates with $(PrS)_2$ thereby transforming each ring system into a bis-propylthiobenzene derivative.

Another interesting experiment Cabbidu performed involved three sequential metalations of both the 1,2,4- and 1,3,5-TMB substrates, where each subsequent metalation was trapped with a different electrophile. First, with monometalation of the TMB Cabbidu's group quenched with the bulky TMS group. A second metalation step was carried out and trapped with $(PrS)_2$, and finally MeI was employed to add the final substituent, a methyl group, to the ring.

Cabbidu also attempted to answer the question as to why it was impossible to metalate three times within the same step. He proposed the same type of argument Sundberg did as to why the anisole or 1,3-DMB would not dimetalate in one step (Figure 12). It can be seen that when the lithium is adjacent to the methoxy on the ring they are

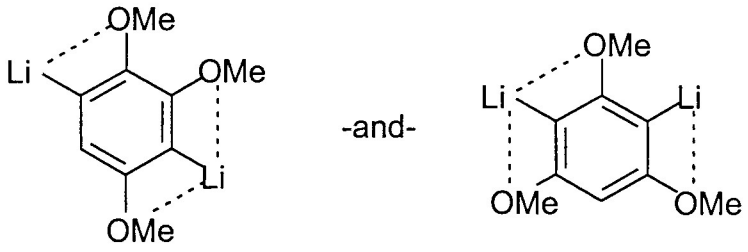


Figure 12. Lithium coordination to adjacent methoxy groups.

still somewhat coordinated. This arrangement will hinder any further coordination by the methoxy group. However, when the lithium intermediate is quenched, once again the methoxy group is free for coordination. In the literature, there are many other references

to the use of DoM to metalate various methoxybenzenes, but these are mainly used in synthesis of larger molecules and will be discussed next.

G. Uses of Metalation : Synthesis

Metalation is frequently found in journals where elaborate organic syntheses are being described. These papers utilize aryllithium reagents prepared by DoM processes leading to large pharmaceuticals and natural products. For instance it is possible to synthetically produce a toleragen to the active ingredient in poison ivy, urushiol 7.[57] In this synthesis a veratrole derivative was metalated to a maximum 73% yield on the way to formation of urushiol 7. 2,3-methoxytoluene was also metalated as a step in the total synthesis of coenzyme methoxatin.[70] A drug used for anti-ulcer, anti-inflammatory research, taspine, can also be produced through the DoM process.[71] The metalation step in taspine synthesis involved formation of a biphenyl. Another drug known to lower blood pressure, babatusol, was also produced by use of ortho-metalation.[72]

These and other examples[73,62] show the impact the metalation reaction can have on the medicinal field, but it can also affect other parts of organic synthesis as well. Albrecht shows how one can elegantly convert a benzaldehyde derivative to a bis-aromatic with an ortho-metalation reaction (Figure 13),[58] and Prevot-Halter can produce

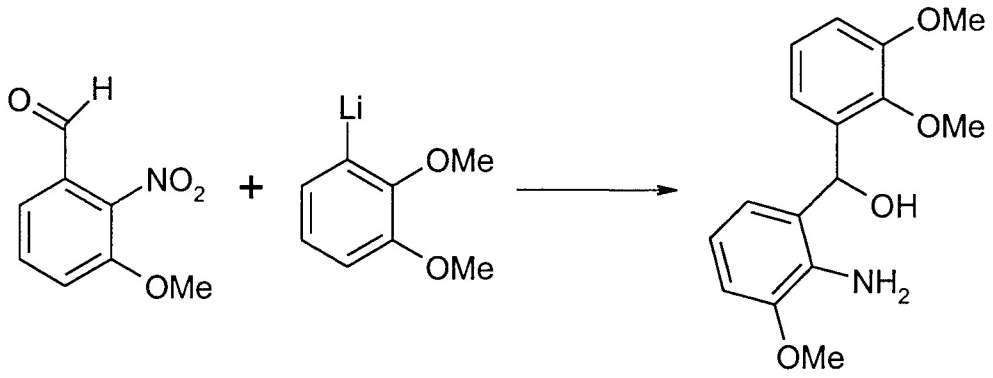


Figure 13. An example of complicated synthesis possible with DoM.

various organic receptors by metalating veratrole as a first step.[59] Not only can the metalation reaction be directly influencing on a reaction but can also have an indirect effect. For instance benzocyclobutenones can be used as intermediates in numerous organic synthesis reactions.[74a-f] According to a procedure by Stevens, the first step to making one of these compounds comes from the bromination of veratrole.[61]

II. RESULTS AND CONCLUSIONS

A. Background

Current views are that the DoM reaction follows two separate limiting mechanisms. One of these involves a prior-coordination complex where n-butyllithium is coordinated to the DMG of the aromatic substrate before lithium/ortho-H exchange takes place. The closeness of the lithium atom to the substrate's ortho-hydrogen facilitates this exchange. In general this type of effect is termed the "complex induced proximity effect" (CIPE).[28] The second mechanism is concerned mainly with the acidity of the ortho-hydrogen. When an electron withdrawing group is situated on an aromatic ring, any protons on the ring will become more acidic with the ortho-protons being the most affected. These acidic protons will be more readily removed by the basic n-BuLi thereby promoting a high rate of regiospecific metalation of the aromatic ring at the ortho-position.

Both mechanisms, however, possess an additional complicating factor in that the n-BuLi can be present in different oligomeric forms, and each form has a different reactivity. Through research already discussed in the introduction it has been found that the n-BuLi dimer is the most reactive. Therefore, in order to achieve the maximum extent of metalation, it is necessary to move the n-BuLi equilibrium to the dimer form through use of coordinating catalysts such as THF, diethyl ether, TMEDA, etc. Each lithium in the n-Butyllithium dimer has two open coordination sites, so the catalyst can

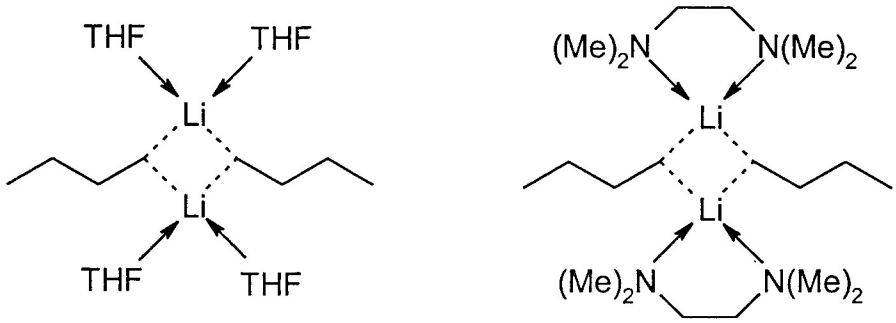


Figure 14. Monodentate and bidentate coordination to n-BuLi.

either coordinate in a monodentate fashion (THF) or a bidentate fashion (TMEDA) as shown in Figure 14. In DoM, the lone pairs from the heteroatom of the DMG coordinate to the alkyllithium, replacing one site where the catalyst was coordinated. In other words, this mechanism involves simultaneous coordination by both the catalyst and the substrate. In such cases, complexation also increases the acidity of the ortho-hydrogens. Both of these factors contribute to the overall CIPE concept.

For substrates such as anisole, a lone pair of electrons on the methoxy substitutent coordinates to a lithium atom in the n-BuLi dimer in a monodentate interaction. Past research in our group, as well as observations reported in the literature, have determined that mono-DMG substrates will not undergo significant metalation in hydrocarbon solvents and addition of a catalyst is necessary.

Multiple DMG's appropriately situated on an aromatic ring could coordinate to n-BuLi in the same bidentate manner as TMEDA. This complexation could promote formation of the complexed dimer intermediate which could lead to observable metalation. In fact, after intense study of ortho- and meta-dimethoxybenzene (o- and m-DMB), such an effect was revealed by observation of significant metalation in

hydrocarbon solvents. The reaction scheme involves the complex induced proximity effect but differs from the metalation of mono-DMG substrates in that no catalyst is necessary to attain high yields, which is only possible when the substrate itself acts as a catalyst. This type of metalation mechanism we term a "substrate-catalyzed" metalation.

B. Discovery of Substrate-Catalyzed Reactions

While exploring conditions for metalation of o-DMB it was found that high yields could be achieved in hydrocarbon media without the addition of a catalyst (Figure 15). This finding led to the concept that sufficient interaction was occurring between the substrate and the n-BuLi oligomers to permit some dimer formation. Our group had also observed results with m-DMB in which moderate metalation in hydrocarbon solvent was achieved with no catalyst present (Figure 16).[75] It has been hypothesized by Saa *et al.*[38] that m-DMB exhibits bidentate complexation of the n-BuLi dimer as a precursor to the eventual ipso metalation--termed the "tweezer" effect as mentioned earlier. It does this by coordinating the n-BuLi dimer in a bidentate manner where both heteroatoms in the dimethoxybenzene are attached to a different lithium atom (Figure 17). If this bidentate

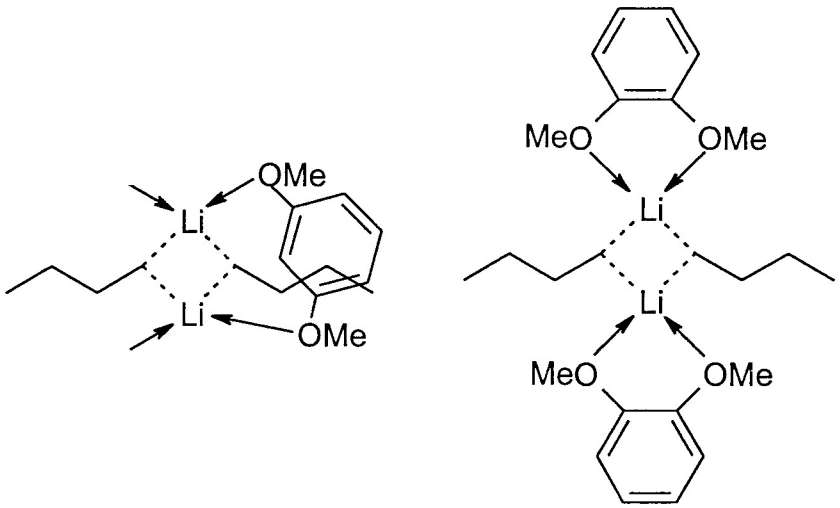


Figure 17. Envisioned n-BuLi dimer stabilization by o- and m-DMB.

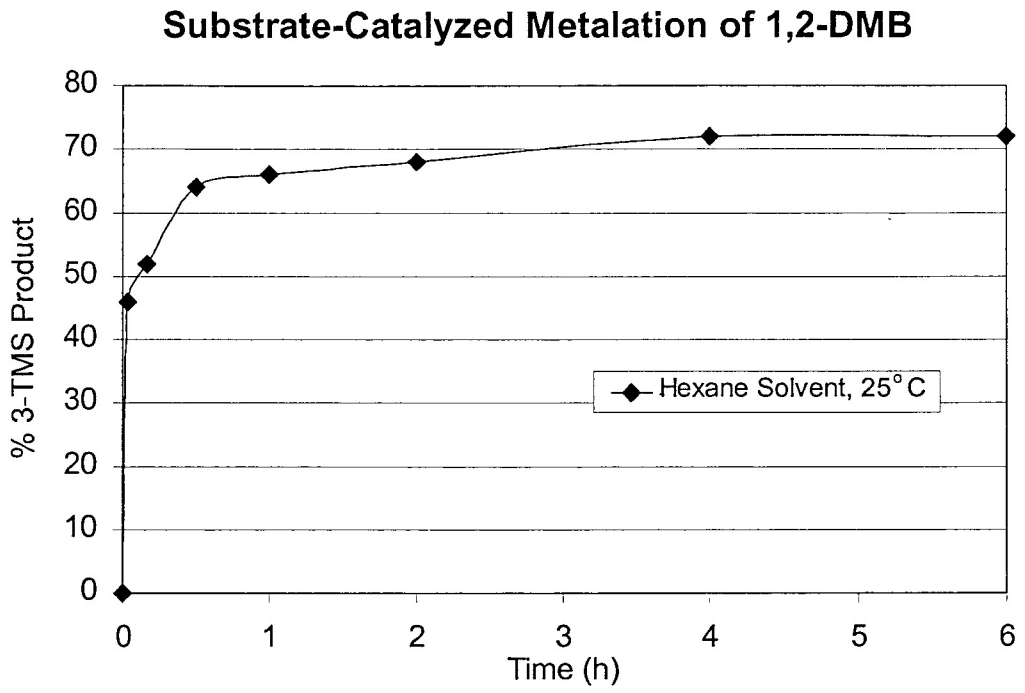


Figure 15. First observed ortho-metlation of 1,2-DMB in a hydrocarbon solvent.

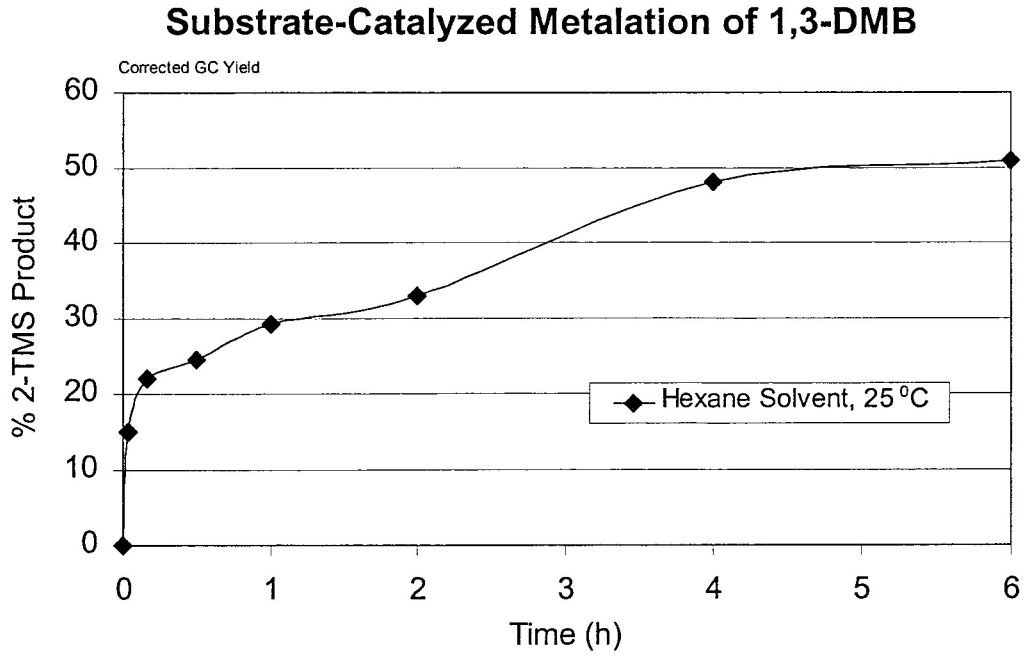


Figure 16. First observed ortho-metalation of 1,3-DMB in a hydrocarbon solvent.

type coordination increases the extent of metalation without any catalyst present, could a similar interaction be taking place with the o-DMB? Envisioned was an interaction with n-BuLi similar to that of TMEDA (Figure 14) where both ortho-substituents coordinate to a site on a lithium atom (Figure 17). As opposed to the m-DMB case, where the substrate forms a bis-coordinated complex attached to both lithiums of the dimer, 1,2-DMB can bis-coordinate a single lithium atom (Figure 14). The hypothesis that such substrate•n-BuLi complexes would enhance metalation is unprecedented. In fact, two recent articles speculate that two methoxy groups ortho to each other on the aromatic ring will sterically interfere with one another thereby decreasing metalation.[76,77] This information is contrary to what we have observed.

C. Project Protocols and Goals

The principal goal of this thesis is to further our understanding of "substrate-catalyzed" metalations in hydrocarbon solvents by completing appropriate studies of 1,2- and 1,3-DMB followed by extension of the protocol to the three trimethoxybenzenes (TMB's). Attempts were to be made, using this concept, to achieve the highest possible yields of metalation of 1,2-DMB, 1,3-DMB, 1,2,3-TMB, 1,2,4-TMB, and 1,3,5-TMB. A small number of papers in the literature report metalations of these substrates; however, an excesses of BuLi and TMEDA (up to six molar equivalents) were used in attempts to di- and trimetalate the aryl substrates.[42,35] This thesis presents a different approach by pursuing a secondary goal which was to afford high yields of the monometalated product while maintaining atom economy[78] through utilization of only one molar equivalent of alkyllithum.

The trapping agent used for the analytical examinations was chlorotrimethylsilane. This reagent has been used for several previous metalation studies and is believed to provide a qualitative estimate of the extent of metalation. Other derivatizing agents were also used for isolation studies.

Another secondary goal was the comparison of the extents of metalation of the DMB's and TMB's in hydrocarbon solvents and in diethyl ether. The solvent cited most often in the literature for metalations is, in fact, diethyl ether. For the over fifty runs recorded in Table I there is only one solvent used: diethyl ether. Our group is of the opinion that ether has held back efficiency of the DoM reaction for years. Ether is definitely not an attractive solvent for industrial use. It is volatile, it forms peroxides and it limits the temperature that reactions can be run (boiling point = 35° C). We also contend that maximum yields are unattainable in diethylether. Demonstration that enhanced extents of metalation can take place in media other than diethylether serves to further our overall objectives.

D. 1,2-DMB

Initial investigations into 1,2-DMB were focused on trying to generate the 3,6-dimetalated intermediate in hydrocarbon solvent. We were relatively successful with approximately a 60% uncorrected GC yield of 3,6-bis-TMS-1,2-DMB being obtained. Through this study we discovered that TMEDA would promote dimetalation more efficiently than other catalysts such as THF, and we could achieve significant metalation under conditions that were much less aggressive than those of Sunberg *et al.*[42] and Cabbiddu *et al.*[35] However, forcing conditions (higher temperatures with excess BuLi) were still necessary, and our attention was turned to a new trend that we were observing.

Metalation without the presence of a catalyst in n-hexane was affording an approximately 80% corrected GC yield of the mono-TMS product. The product was free of contamination by the bis-TMS product. This result deserved some attention, and we found it could be readily repeated in several hydrocarbon solvents (Figure 18).

We also examined several reactions where ether was used as the medium for comparison with our results in which a hydrocarbon medium was employed. No conditions were found where the metalation of 1,2-DMB proceeded as well in ether solvent as it did in hydrocarbon solvent, even when TMEDA catalyst was used. When TMEDA catalyst was added in hydrocarbon solvent we were able to obtain yields comparable to those of the uncatalyzed reaction, but no real improvement was made. Similarly, few citations in the literature report a yield higher than 80% unless excess n-BuLi was used (Table 2).

Just as hydrocarbon solvents seem to afford better yields, they also have a second advantage in that they allow the use of higher reaction temperatures. Attempts were made to metalate 1,2-DMB at high temperatures (60-80°C) to determine whether added energy would enhance metalation. The results were not what one might expect in that some demethylated product was detected. This observation is not without precedence in that Bates *et al.*[46] described a similar demethylation of a series of methoxybenzenes in a highly basic environment. That we observed demethylation under these much less stringent conditions is quite surprising. The n-BuLi/hydrocarbon solutions that were used in our reactions are not nearly as aggressive as the "superbase" (n-BuLi•*t*-BuOK)/reflux environment employed by Bates.[46] Even though our reactions were not run under as aggressive conditions, we conjecture that some organizational feature of the transition

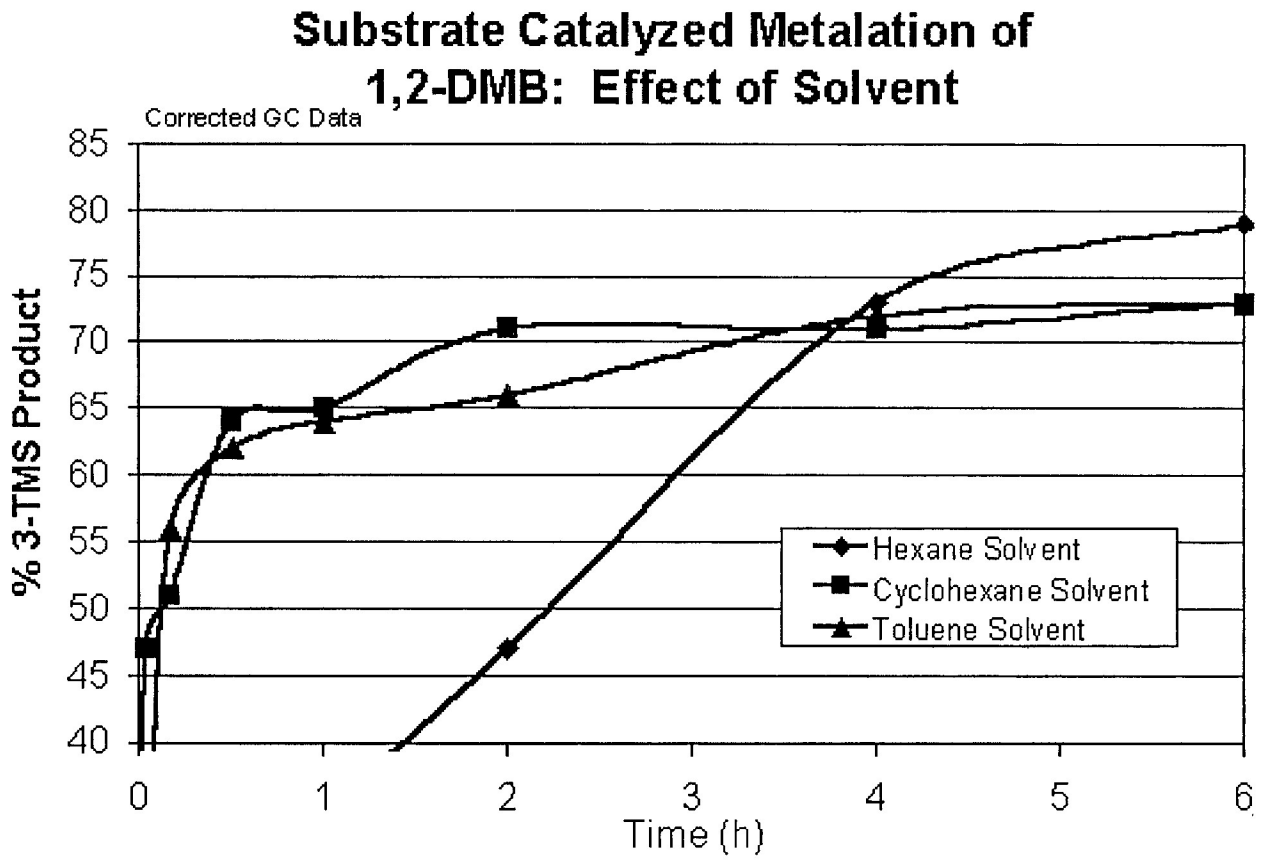


Figure 18. Metalation of 1,2-DMB in various hydrocarbon solvents at 25°C.

state(s) attained under our conditions duplicate those in the transition state(s) achieved under Bates's conditions.

One other complication of note was encountered, namely, the viscous nature of the suspension formed when n-BuLi was combined with the substrate. As soon as the reactants were mixed, the solution became milky and, soon thereafter, turned into a viscous suspension. Our methodology required the use of magnetic stirrers to keep the solutions, even those containing flocculent precipitates, well mixed. At times, a solution became too viscous to stir. This viscosity made initial samples unreliable; sometimes a point could not be taken at all. Over time, however, the suspensions became "looser," usually after about 2 hours, and sampling became possible. Notable differences in this regard were observed for metalations in n-hexane and cyclohexane. Cyclohexane afforded relatively fluid suspensions right from the start whereas metalations in n-hexane did not achieve much fluidity until after 2 hours.

Even though demethylation made the examination of 1,2-dimethoxybenzene at high temperatures unattractive, we were still intrigued that at room temperature significant ortho-metalation could be achieved without the addition of a catalyst. One experiment performed to prove the catalytic nature of the 1,2-DMB substrate was a competitive run between 1,2-DMB and anisole. Under conditions where metalation of anisole afforded little product it was anticipated that the yield would be increased when 1,2-DMB was added. In hexane solvent we did in fact see a doubling of the 2-TMS-anisole yield. This observation supports the hypothesis that 1,2-DMB does in fact act as a catalyst, both inter- and intramolecularly.

E. 1,3-DMB

As previously discussed, for 1,2-DMB higher temperatures can cause problems with demethylation of some of the methoxybenzenes. The TMB's later were found not to undergo demethylation, but no improvement in substrate-catalyzed yield was found with elevated temperature. 1,3-DMB, however, proved the exception; with this substrate higher temperatures brought increased yields of the substrate-catalyzed metalations. Experiments were carried out where 1,3-DMB was metalated at 25°C, 45°C, and 60°C in cyclohexane solvent. Analytical results were gratifying; at higher temperatures the corrected GC yield of the 2-TMS product was elevated (Figure 19). When these results are compared to the initial observations of our group (Figure 16) it can be seen that even at 25°C a 10% higher yield is achieved in cyclohexane than in n-hexane.

Input of energy into the system increased the rate and extent of lithium-hydrogen exchange. Evidently, the 1,3-disposition of substituents demands a more complex transition state that is facilitated by an increase in temperature. Although it is true that an increase in percent yield is observed, the variation for different temperatures is modest. However, significant change is observed in the rates of metalation. At 25°C maximum metalation is achieved in approximately 4h. At 45°C maximum metalation is reached in about 2h, but it only takes about 10 m to achieve a maximum extent of metalation (70%) at 60°C.

The observations of the substrate-catalyzed nature of the ortho metalation of 1,2- and 1,3-dimethoxybenzene in hydrocarbon solvents prompted us to examine this phenomenon in the three trimethoxybenzenes.

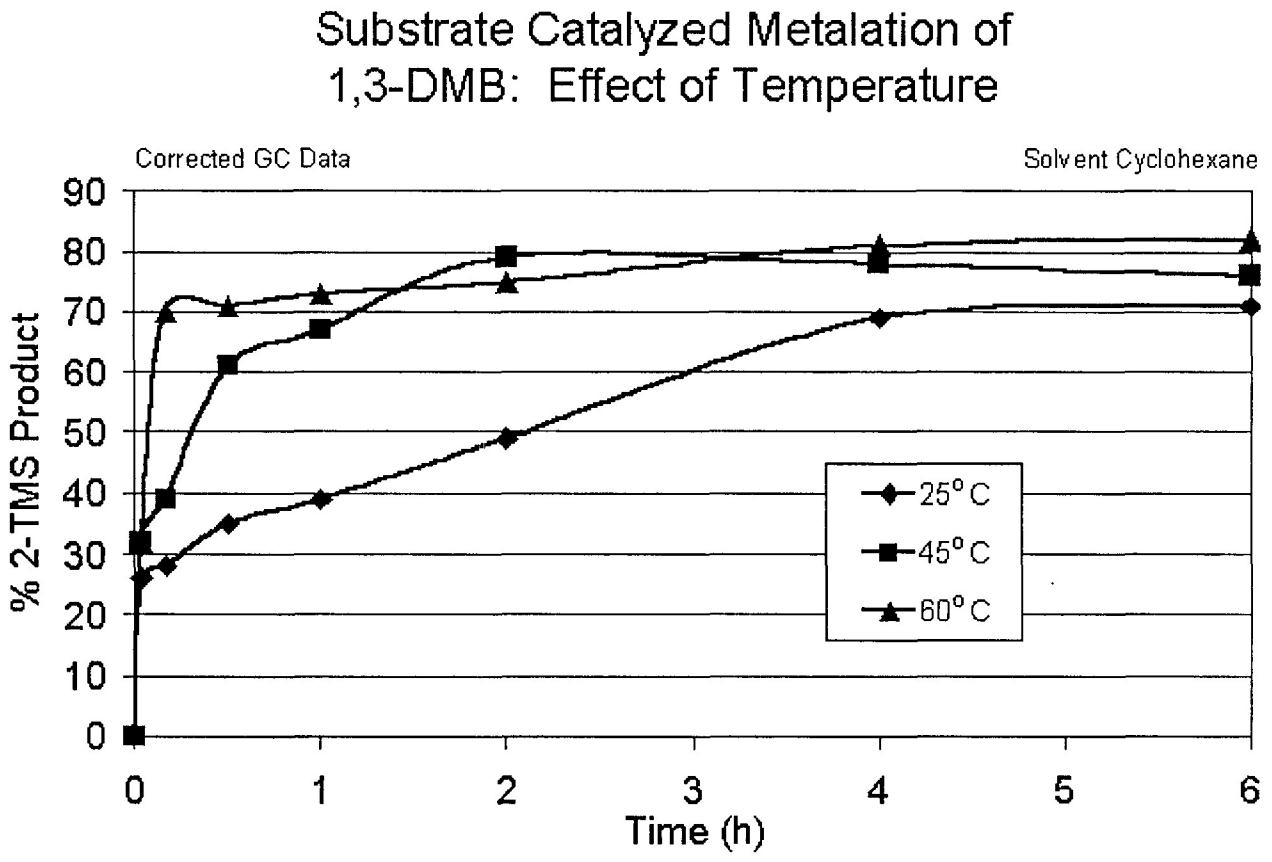


Figure 19. 2-Metalation of 1,3-DMB at various temperatures.

F. 1,2,4-TMB

The 1,2,4-TMB structure incorporates both 1,2- and 1,3- oriented methoxy groups. If our previous conjectures are correct, the ortho-methoxy groups direct lithiation toward the adjacent positions whereas the meta-methoxy groups direct only to the center position. Together, the two systems reinforce metalation at the 3-position which is the product observed in the literature (Table 5). The lithio-intermediate was quenched with ClTMS, and only a mono-TMS product with an M^+ of 240 m/z was observed in the GC/MS. Both substrate-catalysis in hydrocarbon solvents and external catalysis in ether solvents were examined (Figure 20).

The results show that cyclohexane, when using no external catalyst, permits a higher extent of metalation of this substrate than does THF. One surprising result was that MTBE continually supported 5-10% higher extent of metalation (87%) than that obtained in cyclohexane (78%). We have observed for certain other systems that this hydrocarbon-encumbered ether permits high extents of ortho-metalation. Of all the systems studied, the fastest rates of metalation were observed for this substrate; in most solvents maximum extent of metalation was reached within 1 h after addition of the alkyllithium. Toluene afforded a slower rate of metalation wherein about an 80% extent of metalation was reached in 6 h.

Since this rate was the fastest observed for any of the multimethoxy benzenes (MMB's), we decided to experiment with trapping agents other than ClTMS with this substrate. To demonstrate that bulky groups could in fact be substituted at the somewhat inhibited 3-position, the lithio-intermediate was quenched with both benzophenone and phenylisocyanate (Figure 21). The diphenyl carbinol resulting from

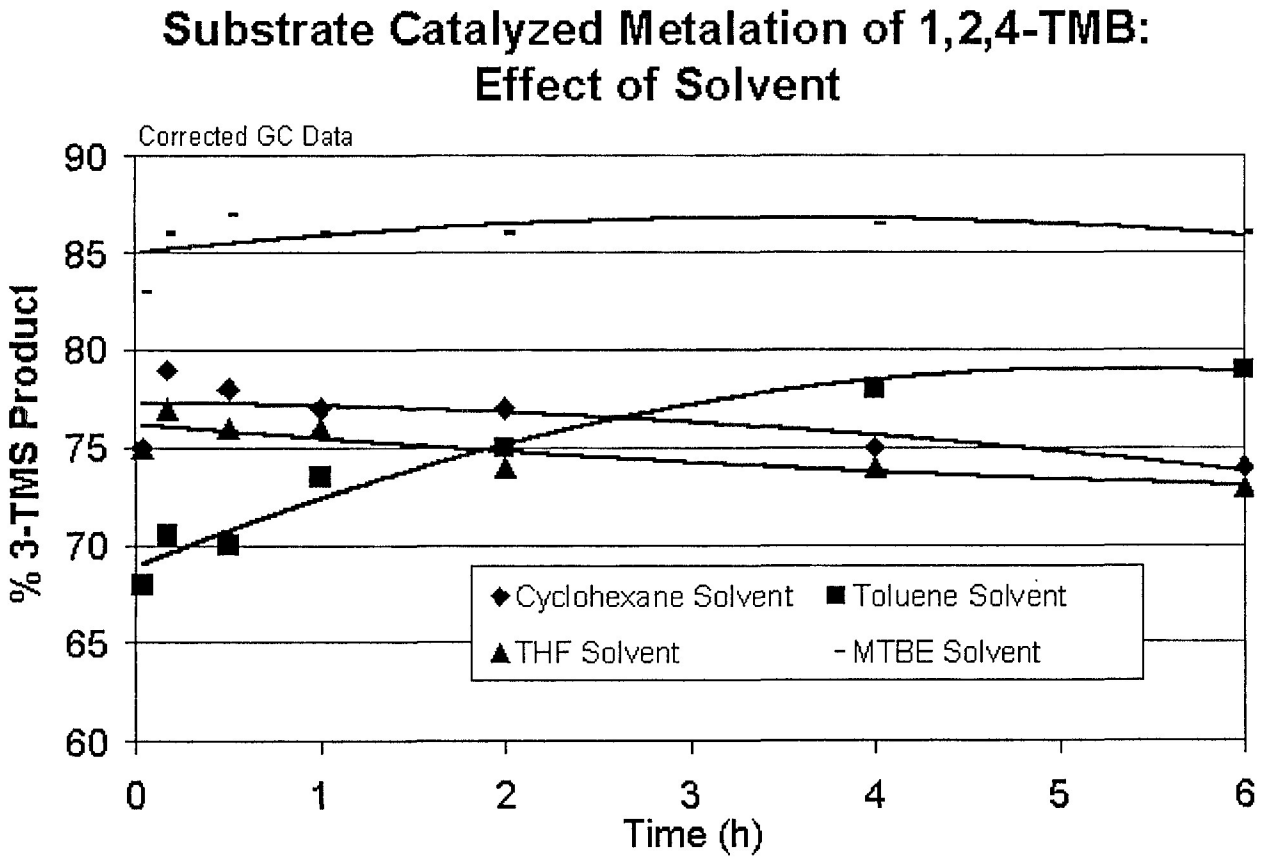
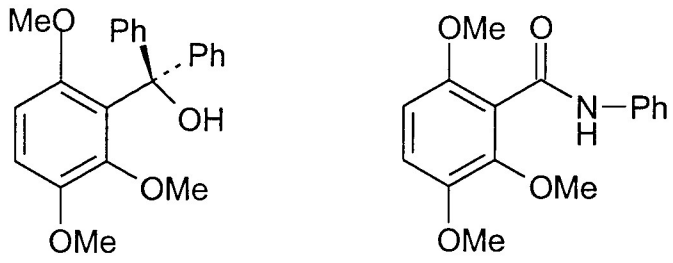


Figure 20. Metalation of 1,2,4-DMB in various solvents at 25°C.



Benzophenone Product Phenylisocyanate Product

Figure 21. Products from quenching 1,2,4-TMB with bulky reagents.

reaction of the lithio-intermediate with benzophenone was isolated and characterized. ^{1}H NMR and elemental analysis data unequivocally supported the identity of the product. The ^{1}H NMR (Figure 22) showed three methyl singlets each integrated to three protons with δ ranging from 3.1-3.8 ppm representing the methoxy groups and a doublet of doublets at 6.6-6.9 ppm representing the two remaining aromatic protons on the TMB ring. Ten more protons in the aromatic region were assigned to the two phenyl groups.

Elemental analysis for percent carbon, oxygen and hydrogen match within an acceptable range with the calculated theoretical values. In fact, elemental analysis results for carbon (75.28%) and hydrogen (6.01%) differed from the theoretical values by 0.13% and 0.32%, respectively. The crystals were produced in 68% yield, and a sharp melting point of 104.5-105°C was also observed.

The phenylisocyanate product was characterized with relative ease. The ^{1}H NMR (Figure 23) exhibited three equal singlets representing the nine methoxy group hydrogens. An aromatic doublet of doublets was observable similar to that of the benzophenone quench. Integration of the aromatic protons was slightly high showing nine protons in the aromatic region where only eight protons are expected (seven aromatic and one amide proton(s)). To further the confirmation of the assigned structure

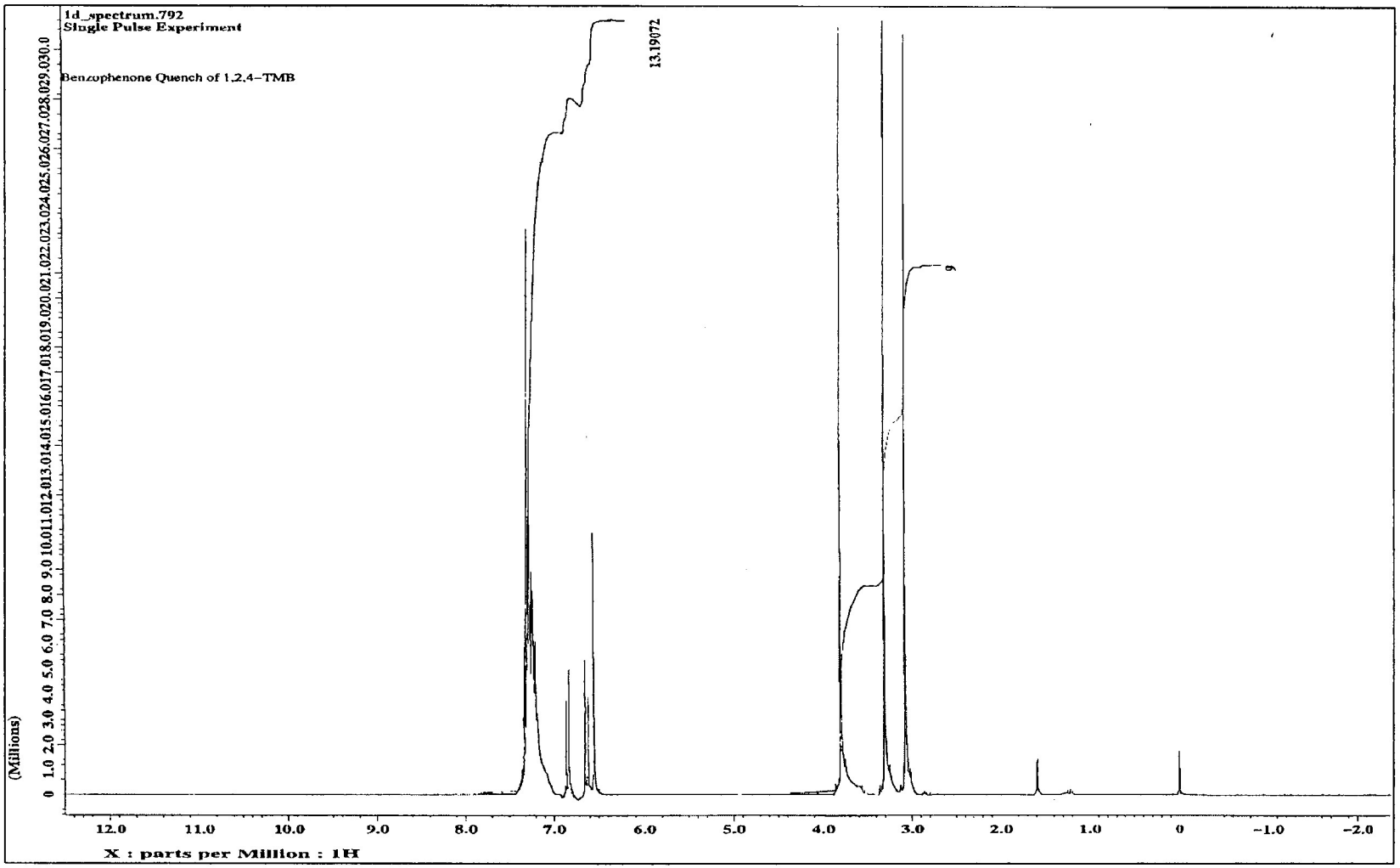


Figure 22. ^{1}HNMR of the benzophenone derivative of 1,2,4-TMB.

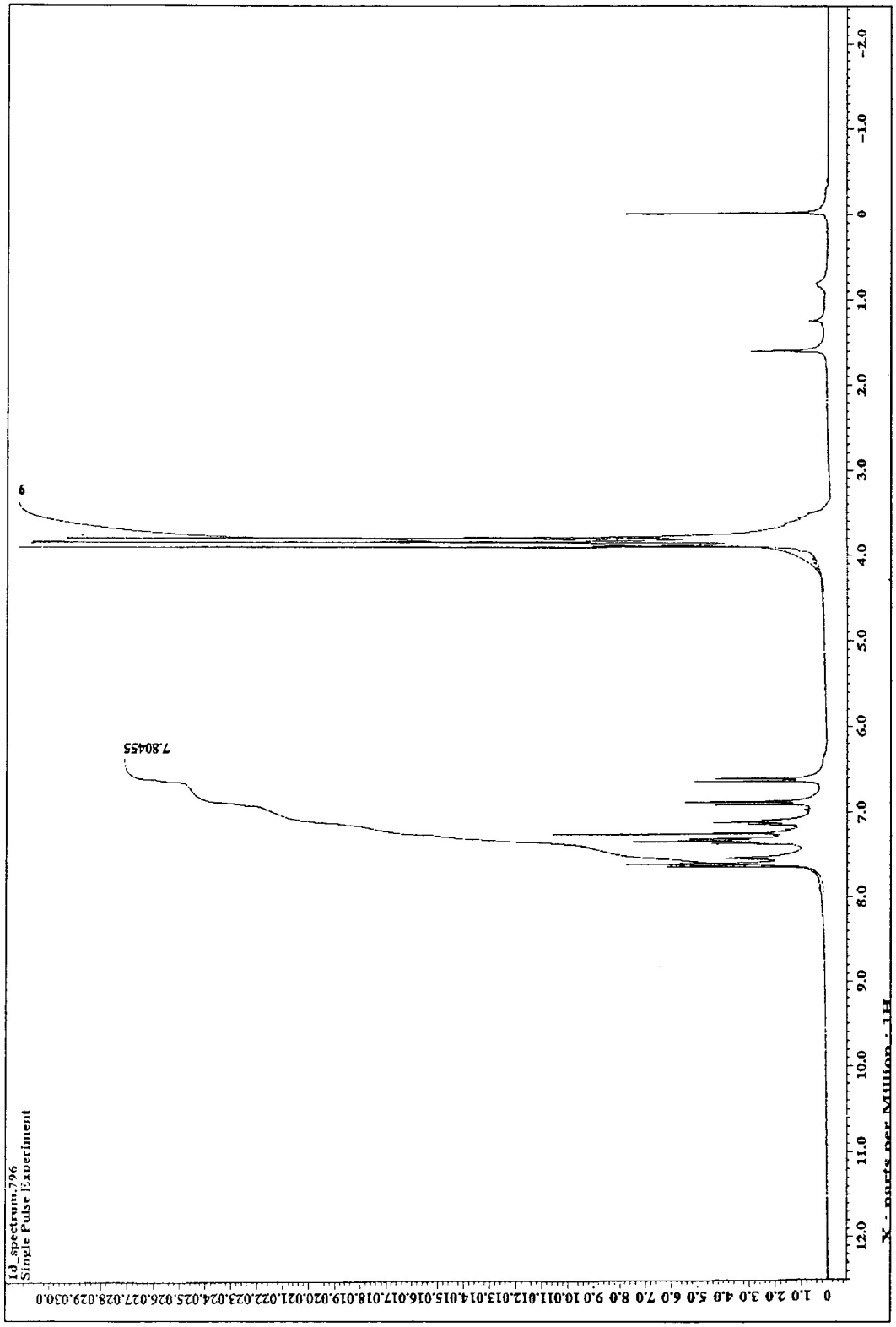


Figure 23. ^{1}HNMR of the phenylisocyanate derivative of 1,2,4-TMB.

a ^{13}C NMR (Figure 24) was examined; it showed all fourteen carbon peaks. Between 56 and 62 ppm, three observable signals were found and were assigned to the three methoxy carbons. The ten aromatic carbons shifts range from 106.61 to 150.87 ppm. The remaining signal at 163.33 ppm was assigned to the carbonyl carbon.

Elemental analysis was also performed on the phenylisocyanate derivative of 1,2,4-TMB, and the results were in accord with the calculated percentages. A percent carbon of 66.55% was found compared to the calculated percentage of 66.89%, and nitrogen was also acceptable with only a 0.27% discrepency from theoretical values. The crystals were produced in 70%, and a melting point range of was 149.5-150.8°C as attained.

G. 1,2,3-TMB

This metalation was anticipated to occur at the 4-position with possible dimetalation at the 4- and 6- positions (Table 4). Production of 1,2,3-trimethoxy-4-trimethylsilylbenzene (M^+ = 240 m/z) occurred as expected in 68% corrected GC yield (Figure 25). Also illustrated in Figure 25 is a time plot of the formation of a second product which possessed a mass of 194 m/z by GC/MS analysis. Production of this side reaction reached only a maximum of 20% in 1 hour, but a detailed study needs to be carried out to identify the structure of this product. There has been successful metalation of the 1,2,3-TMB substrate in the literature but no side product is reported.[42] Aside from this secondary product, no products from dimetalation or any other side-reaction were observed.

The mass spectrum of this unknown product contained a major fragment at 151 m/z which corresponded to a tropylium ion containing two methoxy substituents. This

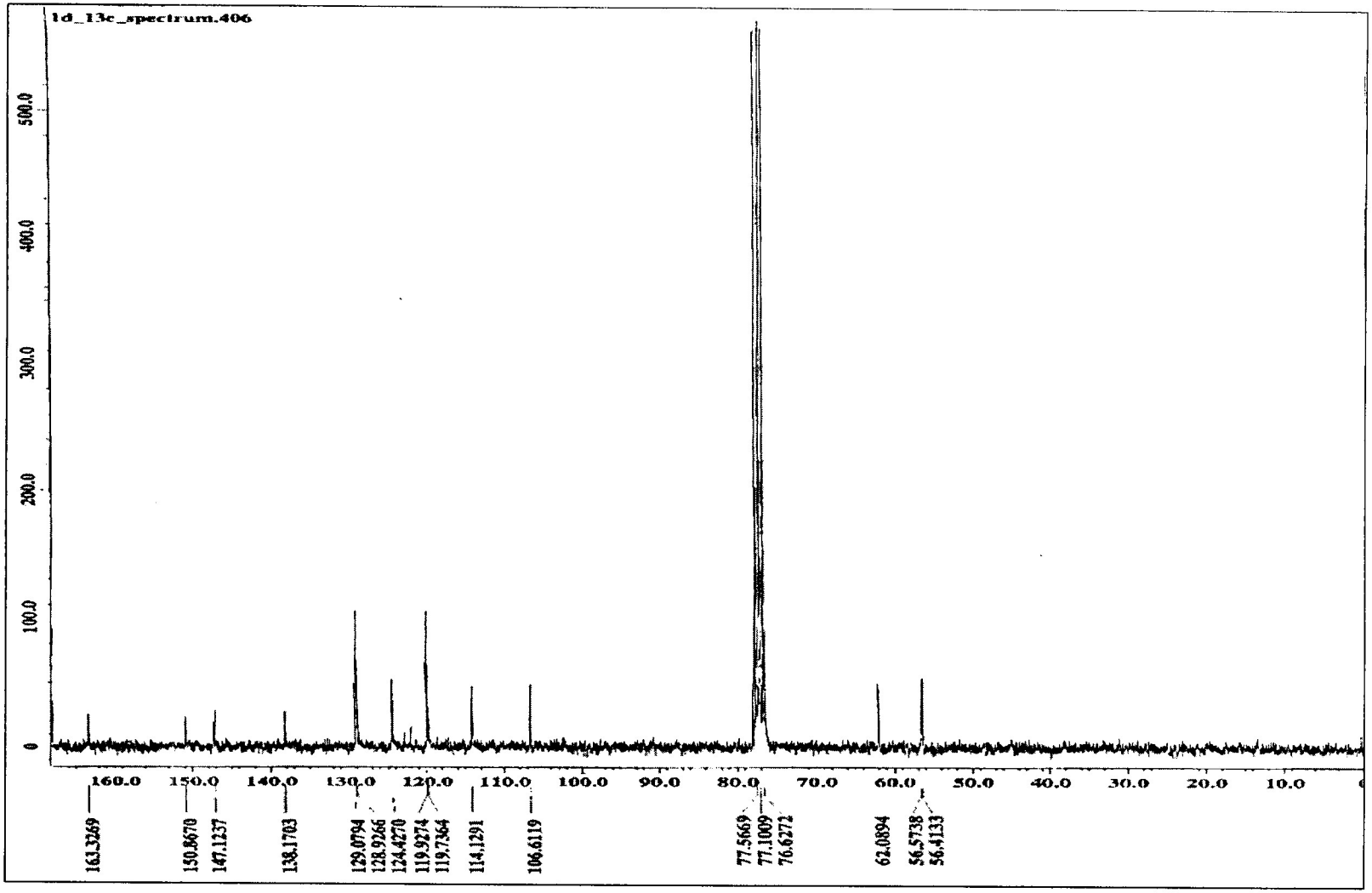


Figure 24. ^{13}CNMR of the phenylisocyanate derivative of 1,2,4-TMB.

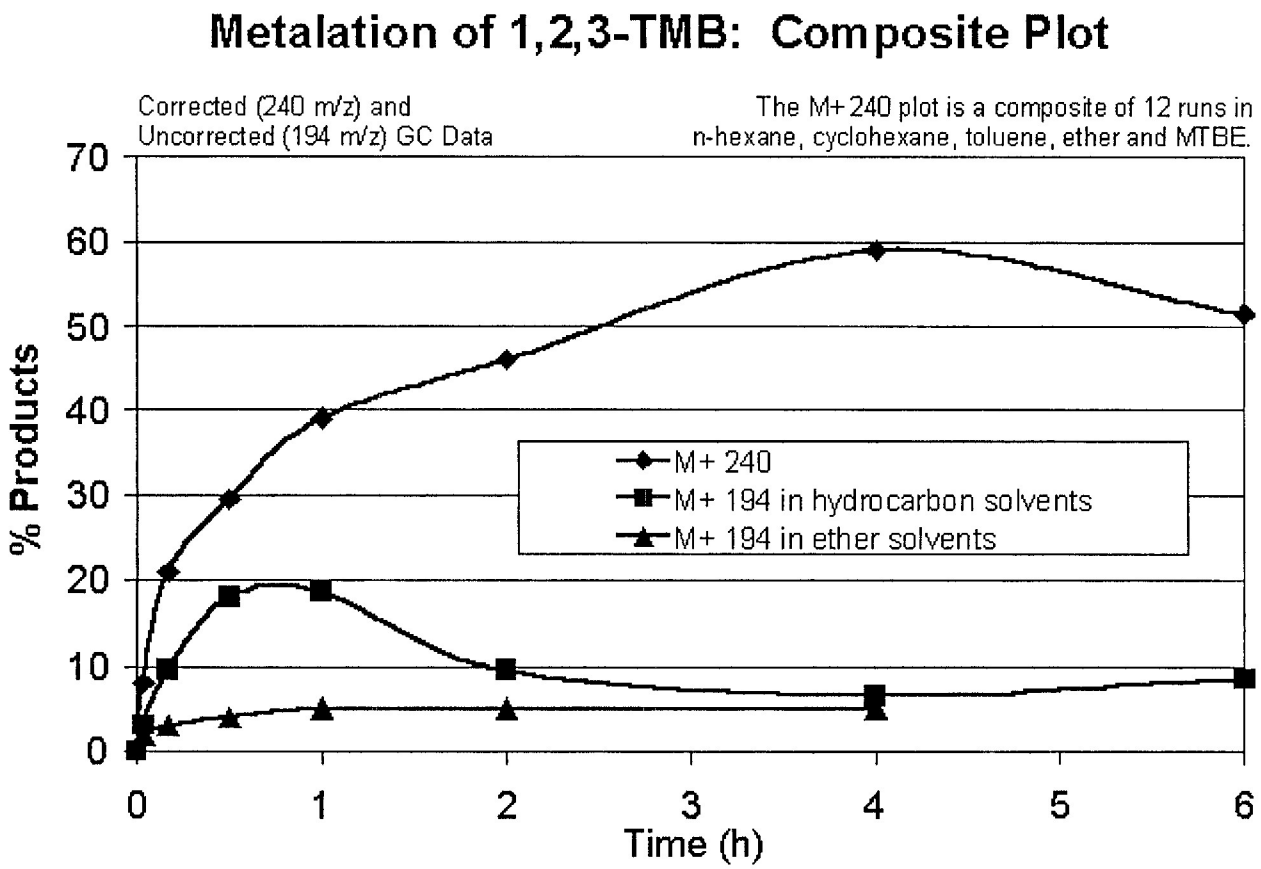


Figure 25. Metalation of 1,2,3-DMB in ether and hydrocarbon solvents.

fragment indicated the presence of a benzyl carbon and the loss of a methoxy group. Following this line of reasoning, we concluded that a butyl anion from the alkyllithium had displaced a methoxy group resulting in a butyl dimethoxybenzene with an m/z equal to 194. Displacement of a methoxy group from an aromatic ring is not intuitive but neither is it unprecedented; several papers report just such an occurance.[79,80]

The remaining question was which methoxy group had been replaced. Chemical intuition told us that it was the center methoxy group that was lost since it would be the one more vulnerable to nucleophilic attack. This by-product was isolated, purified and an ^{13}C NMR was obtained for verification (Figure 26). From this spectra we saw nine different carbon peaks: four from the butyl group (14.16, 22.75, 22.98 and 31,64 ppm), four from the aromatic ring (103.78, 119.76, 126.44 and 158.41 ppm), and one from the symmetrical methoxy groups (55.76 ppm). If a peripheral methoxy group had been displaced, the symmetry of the system would have been lost, and twelve different carbons signals rather than nine would have been observed. ^{1}H NMR shows equally convincing spectra.

One last concern needs to be addressed for the 1,2,3-TMB substrate. Referring once again to Figure 25, it can be seen that the formation of the second product was somewhat dependent on whether the solvent is an ether or a hydrocarbon. Ether solvents apparently reduce formation of the ASN displacement of the 2-methoxy group. Conjecture as to a reason for this observation involves a mechanism where the two outer methoxy groups are coordinated to the the n-BuLi dimer in manner similar to that in the 1,3-DMB (Figure 27). Positioning the molecules in this fashion will place the nucleophilic carbon on n-BuLi directly in line with the positive end of the dipole of the

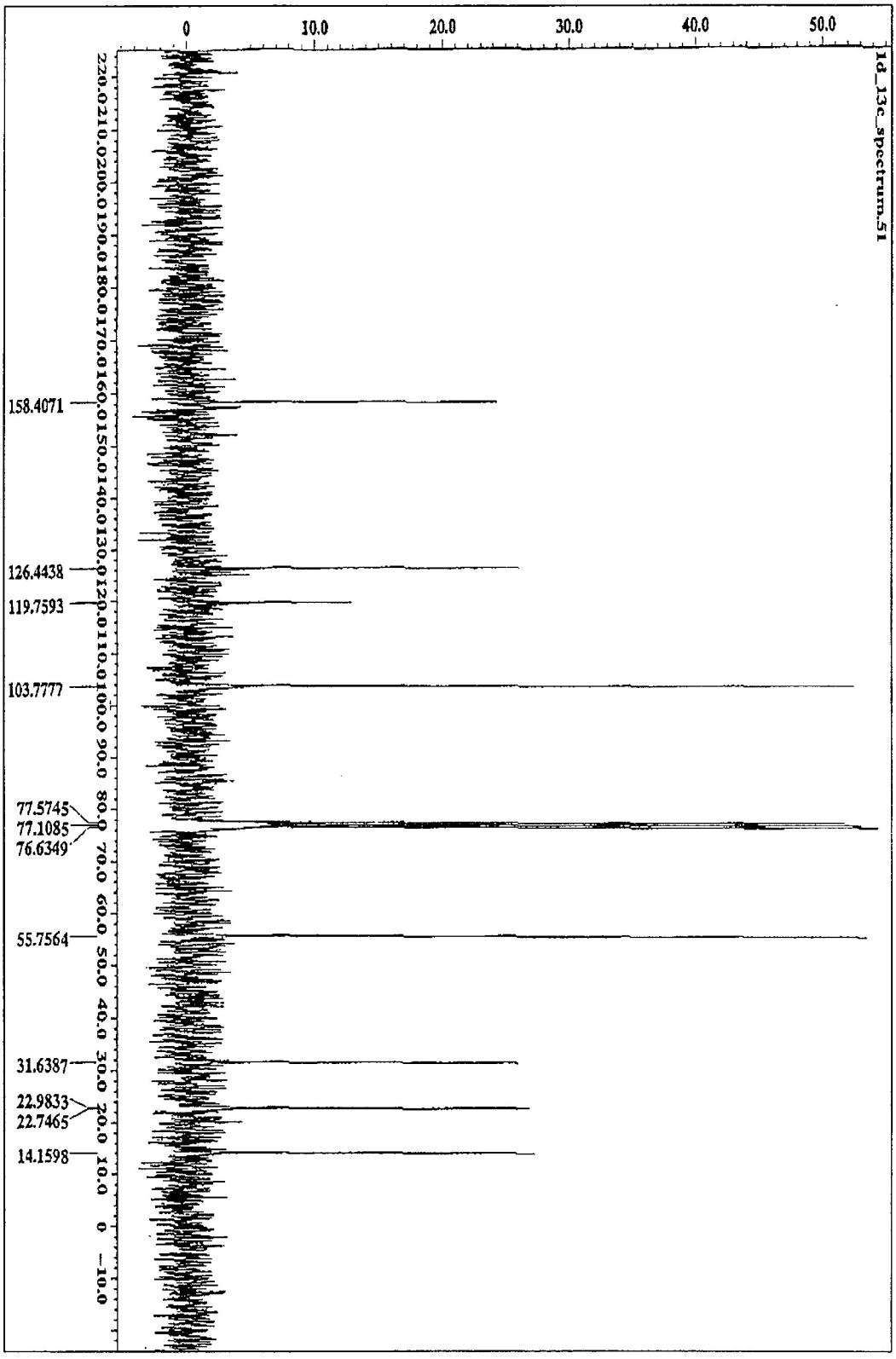


Figure 26. ^{13}CNMR of 2-butyl-1,3-dimethoxybenzene.

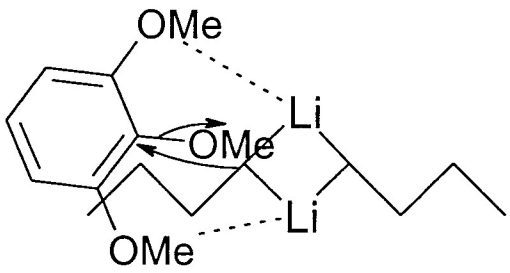


Figure 27. Conjectured mechanism for displacement of the center methoxy group in the reaction of 1,2,3-TMB with n-BuLi.

aromatic C-O bond, thereby facilitating the observed displacement. Therefore when ether solvent is present it will interact with the n-BuLi dimer, disrupt formation of this intermediate state and effectively lower the yield of this product. On the other hand, when hydrocarbon solvents are employed, solvent coordination is absent and this intermediate can form more readily.

H. 1,3,5-TMB

1,2,4-TMB performed impressively under substrate-assisted metalation conditions, and 1,2,3-TMB perfomed well and also gave an interesting and unexpected result under such conditions. 1,3,5- TMB, however, does not exhibit the phenomenon we call substrate-assisted metalation. Yields no greater than 5% were attained in cyclohexane, n-hexane, toluene and MTBE solvents. One explanation for this result is the insolubility of this substrate in hydrocarbon solvents before the addition of n-BuLi. Even after the addition of n-BuLi the solution becomes flocculent forming a heterogeneous mixture. Some substrates already discussed have slight solubility problems and form thick solutions upon addition of n-BuLi, but none to the same extent as that of 1,3,5-TMB.

Another explanation for the unreactivity of this substrate may be found in some subtle electronic effect. 1,3,5-TMB is very similar to 1,3-DMB which undergoes metalation in hydrocarbon solvents quite readily, yet 1,3,5-TMB does not. Similarly, 3-methoxydimethylaniline would be expected to undergo facile substrate-assisted metalation, but this substrate fails to undergo metalation in hydrocarbon solvents even with catalysts present.[81] It is therefore possible that subtle electronic effects may be altering the reaction in a way that is currently unknown to us.

When catalytic TMEDA is added to the 1,3,5-TMB in hexane solvent the solution is much better behaved, and metalation and derivatization proceed in good yield (Figure 28). The literature contains several examples of successful metalation of 1,3,5-TMB, but ether solvents are always used (Table 6).

I. Conclusions

Since substrate-assisted catalysis has now been demonstrated, its utility in organic synthesis can be assessed. Under the conditions possible for this reaction the external catalysts could be eliminated and the complexity of the DoM reaction would be dramatically reduced. The problem is that the requirements for the substrate structure for this specific type of DoM reaction are very strict. For example, while 1,3,5-TMB and 1,3-DMB are very similar in structure, 1,3,5-TMB will not successfully undergo metalation under substrate-assisted conditions, whereas 1,3-DMB does so efficiently. This fact limits the number of substrates where this protocol can be used, but the fact remains that under the right conditions substrate-assisted metalation can be useful.

The results that we obtained revealed some interesting insights into DoM reations involving the MMB's. The initial observation of substrate-assisted catalysis occurred

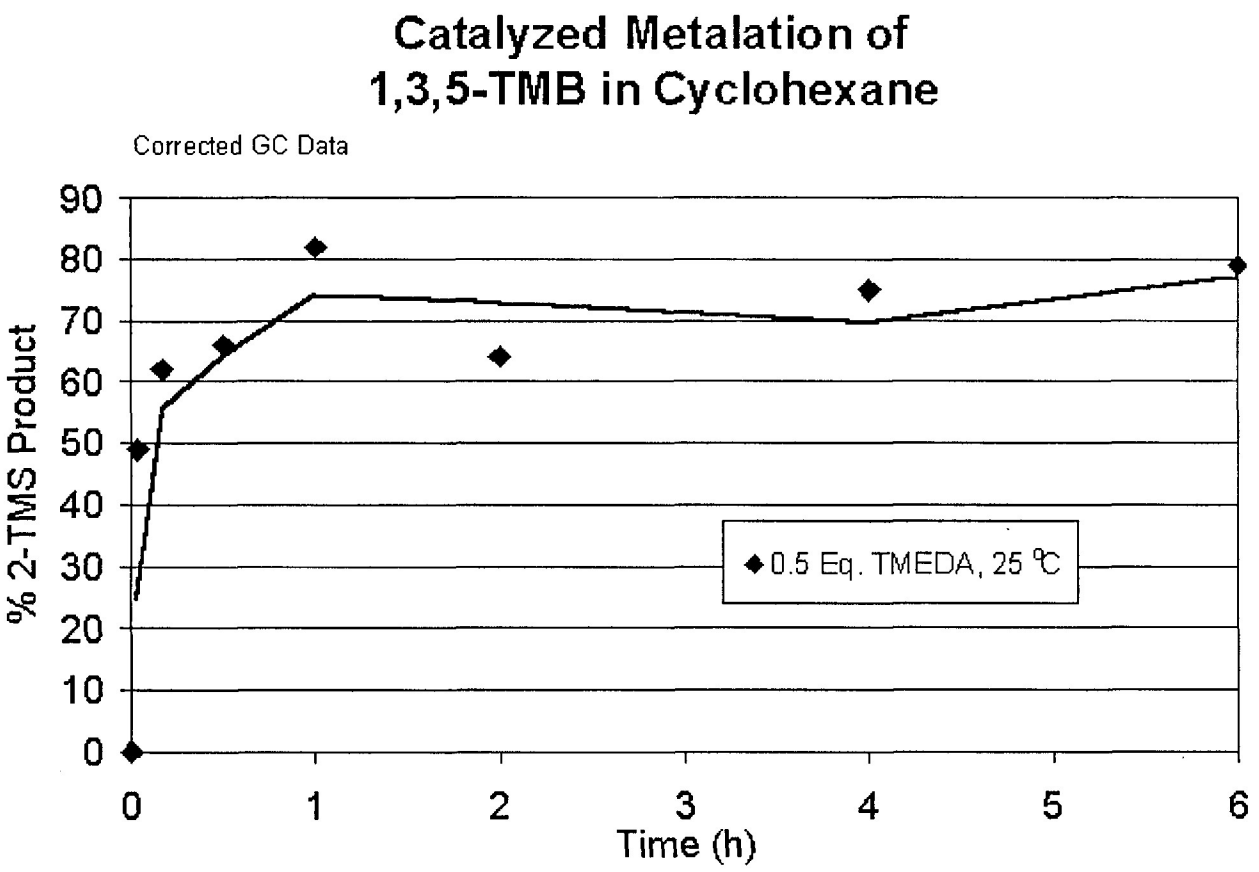


Figure 28. Metalation of 1,3,5-TMB with TMEDA catalyst.

with the 1,2- and 1,3-DMB substrates. Both of these were able to support substrate-assisted catalysis efficiently, thereby leading to experimentation with the TMB's which afforded varying results. 1,2,4-TMB underwent DoM very well and displayed a rapid rate of metalation. Further experimentation was done on this compound leading to reactions with the bulky benzophenone and phenylisocyanate quenching agents. Even considering the size of these reagents the derivatizations were successful and these products were isolated.

1,2,3-TMB was also examined and found to undergo substrate-assisted metalation in good yield. A side product was found and was proven to be that from replacement of the center methoxy group on the aromatic ring by a butyl group.

Comparison of our substrate-assisted protocols with the aromatic metalation procedures commonly used in research suggests that there are some definite advantages to our methodology. One of these advantages lies in the ion-multiple selectivity of the substrate-catalyzed DoM reaction. Under such conditions, the four substrates exhibiting substrate-catalyzed metalation afforded only mono-lithiated products; other researchers, under different conditions, produce di- or tri-lithiated products.[35,42] Although some researchers are purposefully seeking such products, limitation to the mono-lithiated product has been proven possible through our methods.

A second advantage to our methodology is found in use of hydrocarbon solvents where ether solvents have been used predominantly in the past. As has already been pointed out, there are many hazards to use of ether solvents in industry. Another disadvantage that we have observed is that the classical ether solvents do not support as efficient metalation as do hydrocarbon solvents. We also find a third advantage in the

atom-economy of the system. Little waste is produced since side-products are limited, no catalyst is used and high yields (>80%) can be obtained for most of the MMB's.

Four variables effect how well a DoM reaction will undergo metalation: DMG coordinating ability, DMG electronic effects, the medium and steric effects. We believe that through these different contributions there are an array of accessible transition states for the DoM reaction. This complexity may compromise efficient DoM. Utilizing the substrate-assisted methodology keeps the metalation system simple, and many of the confusing factors that occur when catalyst and ether solvent are present disappear. DoM is an intricate and multifaceted process; through this investigation additional insight into its controlling features has been gained.

III. EXPERIMENTAL

A. Reagents

All reagents were obtained from Aldrich Chemical Company unless otherwise indicated. Early work in this project was completed with pre-standardized 1.6 M n-BuLi donated by the FMC Corporation. Other reagent-grade n-BuLi was purchased in three different concentrations: 10 M in hexanes, 2.5 M in hexanes, and 2.0 M in cyclohexane. No standardization of these reagents was performed. All of the alkyllithium reagents were stored in a refrigerator. 1,2- and 1,3- Dimethoxybenzene were purchased and used without further purification as were the three possible trimethoxybenzenes (1,2,3-, 1,2,4- and 1,3,5-trimethoxybenzene). 2.0 M solutions of the primary trapping agent, chlorotrimethylsilane (Cl-TMS) in n-hexane, were dried over 4 Å molecular sieves and stored in the refrigerator.

Tetrahydrofuran (THF) was also dried over 4 Å molecular sieves. n-Hexane, cyclohexane, *tert*-butyl methylether, and toluene (the various solvents used) were dried over $MgSO_4$ or 4 Å molecular sieves. The diethylether used in a small portion of the reactions was purchased from EM Scientific and dried over 4 Å molecular sieves. Ethanol, used for recrystallization, was purchased from EM Scientific and used without further purification.

B. Instrumental

All gas chromatography (GC) data was collected with a HP 5890 instrument using a flame ionization detector in conjunction with an OV-17 packed column. The injector

and detector were maintained at a constant 250°C temperature. The column oven temperature, initially set at 120°C, was ramped at a rate of 15 degrees per minute to a final temperature of 225 to 250°C, by which temperature all peaks were observed. The area of the peaks were calculated using digital integration. Some of the average retention times observed for the methoxybenzenes and TMS derivatives are compiled in the following table:

Table 7. Gas Chromatography Retention Times of Relevant Compounds.

Name of Compound	Retention Time (min.)
1,2-Dimethoxybenzene	2.43
1,3-Dimethoxybenzene	2.20
1,2,3-Dimethoxybenzene	3.72
1,2,4-Trimethoxybenzene	4.27
1,3,5-Trimethoxybenzene	4.26
3-TMS-1,2-Dimethoxybenzene	3.79
2-TMS-1,3-Dimethoxybenzene	3.90
4-TMS-1,2,3-Trimethoxybenzene	5.00
3-TMS-1,2,4-Trimethoxybenzene	5.20
2-TMS-1,3,5-Trimthoxybenzene	5.49
2-n-Butyl-1,3-Dimethoxybenzene	4.45

The column pressure was approximately 30 plus or minus 10 psi.

NMR spectra were obtained on a JOEL TSX 270 MHz FTNMR with multinuclear capabilities. A Mel-Temp II instrument was used to obtain all melting points without correction. Gas Chromatography/Mass Spectrometry data was collected with a HP 5890 GC in conjuction with a 5970 Mass Selective Detector.

C. Standardization of the GC Spectra

The first step in the determination of the correction factor was the isolation of the TMS derivative. A weighed sample of the isolated material was diluted to 50 mL in n-

hexane solvent using a volumetric flask, and the solution's molarity was calculated. A similar solution of the starting material was then prepared obtaining a molarity as close to the molarity of the product solution as possible. Mixtures of the starting material solution and the product solution were prepared in calculated molar ratios of approximately 1:5, 2:4, 3:3, 4:2 and 5:1, respectively. A gas chromatogram was then obtained for each of the above five mixtures. Data obtained was plotted on a chart of area ratio (starting material : product) vs. the molar ratio (starting material : product). The result was a straight line, the slope of which is the correction factor. The final equation for the corrected gas chromatographic yield was as follows:

$$\% \text{ Corrected Yield} = \frac{\text{Correction Factor} \cdot \text{Product Peak}}{(\text{Correction Factor} \cdot \text{Product Peak}) + \text{Sum of Other Peaks}}$$

D. Sampling Techniques

One milliliter samples were taken using either a 5 or 10 mL glass syringe with a 12", 18 gauge needle. This sample was then injected into a 10 mL sample vial in which excess THF was already present. The vial was capped and vigorously shaken then set aside for further analysis. In order to obtain representative samples of solutions containing particulate matter, the suspension was rapidly stirred using a magnetic spin bar.

In reactions where significant pressure developed inside the reaction vessel, the excess pressure was purged by insertion of a 1" needle into the septum. If this precaution is not taken excess pressure would expel most of the sample from the needle before transference to the sample vial could be successfully completed. Samples were taken by putting the needle all the way to the bottom of the flask and withdrawing one milliliter of

the solution. The spin bar needed to be restarted after each sample was taken because the sampling needle disturbed stirring. In some instances heavy precipitates were formed and samples were taken carefully avoiding disturbance of the spin bar. At other times reactions actually became so thick that no samples could be taken.

E. General Metalation Procedures

1. Diethyl ether

Ether has historically been the classic solvent for use in ortho-metalations, but our own program has tried to phase out use of this potentially explosive reagent. However, for comparison purposes, a few runs were carried out using ether as the solvent. 0.02 or 0.04 mol/eq. of the substrate was added to 30 mL of diethyl ether contained in a round bottom flask. The 200 mL, one-neck flask was sealed with a rubber septum and the atmosphere of the reaction vessel purged with nitrogen. In addition to the chemical contents of the flask a magnetic spin bar was placed within the liquid in order to insure proper mixing of the solution.

The reaction vessels were placed in a constant temperature water bath held at 25°C. Since bottles of BuLi in ether solvents was commercially unavailable, addition of 10 M n-BuLi to the ether was necessary. 10 M n-BuLi is not totally free of alien solvents but contains a very small (about 33%) amount of hexanes. Upon addition of the one or two molar equivalents of 10 M n-BuLi, 1.0 mL samples were taken at various times: 2 min, 10 min, 30 min, 1 hr, 2 hr, 4 hr, and 6 hr. The samples were placed into a sample vial already containing 1.0 mL of 2 M Cl-TMS in dry hexane (the quenching reagent used). Yields were attained for runs in neat solvent and also for runs containing incremental amounts (0.01 to 2.0 mol/eq.) of TMEDA. Workup of the TMS-product

involved addition of hexane and $Na_2CO_{3(aq)}$. A 1 μL aliquot of each sample's organic layer was analyzed by GC.

2. n-Hexane

The conditions varied more in hexane solvent than in ether solvent. These reactions had the same basic setup, but slight changes were made in order to optimize efficiency. Since n-hexane is less volatile than ether, more freedom was available for temperature variation with runs being made at 25°C, 45°C and 60°C. These experiments were performed in various concentrations with the majority of runs at either 0.02 or 0.04 mol/eq. of substrate, but 0.01, 0.03, and 0.05 mol/eq. were also examined. Catalysts (TMEDA, THF) were also added to promote the metalation process. Dry THF was added in volumetric amounts of 1 to 8 eq. and TMEDA was added in 0.01 to 2.0 eq.

While 30 total mL of solvent were utilized, one must realize that some of that solvent comes from the BuLi reagent. These reactions were started with 1.6 M and 2.5 M n-BuLi in hexanes. To maintain 30 mL of solvent the added n-hexane was actually equal to 30 minus the volume from the n-BuLi reagent. Workup of these product solutions was identical to the procedure used for those run in ether solvent.

3. Cyclohexane

The procedure used with cyclohexane solvent was the same as that for the metalation in n-hexane except 2.0 M n-BuLi in cyclohexane was added instead of the 2.5 M n-BuLi in hexanes.

4. Toluene, Neat THF and MTBE

Procedures similar to those previously described were utilized. The only significant difference is in the concentration of the n-BuLi reagent. Again, since we have

no comercially available n-BuLi in these solvents, 10 M n-BuLi was added. Toluene systems were run at 0.02, 0.03 and 0.04 mol/eq. amounts where additional amounts of THF were added as promoter. Each of the toluene runs was performed at 25°C. Neat THF reactions were also run at 25°C, but heated reactions at 45°C, and 60°C were also examined. These runs were carried out at concentations of substrate of 0.02, 0.03 and 0.04 mol/eq. Finally, MTBE systems were run at 25°C, 45°C and 60°C temperatures at concentrations of 0.02 or 0.04 mol/eq.

F. Derivatizations

1. 3-TMS-1,2-DMB, 2-TMS-1,3-DMB, 3-TMS-1,2,4-TMB, 4-TMS-1,2,3-TMB, 2-TMS-1,3,5-TMB

1,2-DMB, 1,3-DMB, 1,2,3-TMB, 1,3,5-TMB and 1,2,4-TMB were each reacted with equivalent amounts of n-BuLi. These reactions were done in various temperatures (25°C, 45°C , 60°C , and at reflux). The lithium intermediate was then quenched with excess Cl-TMS producing the appropriate TMS product. These compounds have all been previously examined through a related process.[42] Mass spectra of each of these derivatives were indicative of the structures already determined.

2. 1,3-Dimethoxy-2-n-butyl-benzene

This side product is a major one formed upon addition of one molar equivalent of 1,2,3-TMB to one molar equivalent of n-BuLi under several sets of conditions. It was isolated as an oil through purification by flash chromatography. A one gram column was used with silica gel and a development solvent of 15% ethyl acetate in hexane. MS: m/z (%), 194(M^+, 20), 151(M^+ - C_3H_7, 100), 91(M^+ - $C_6H_{15}O$, 35); ^1H NMR: δ 0.91(t, 2.69 H), δ 0.40(m, 3.63 H), δ 2.65(t, 1.79 H), δ 3.82(s, 6.00 H), δ 6.52(d, 1.74 H), δ 7.11(t,

0.90 H); ^{13}C NMR: δ 14.16, δ 22.75, δ 22.98, δ 31.64, δ 55.16, δ 103.78, δ 119.76, δ 126.44, δ 158.41

3. Benzophenone Derivative of 1,2,4-TMS

A one to one molar ratio of 1,2,4-TMB to n-BuLi at a concentration of 0.04 mole/eq. in 30 mL of n-hexane and 25°C was initiated. After 1.5 h the lithium intermediate was quenched with excess benzophenone dissolved in n-hexane. Workup with Na_2CO_3 and hexane was carried out and the organic layer was analyzed. Upon evaporation of the n-hexane solvent a crystalline product was isolated. Fractional crystallization with ethanol produced a pure white powder which was isolated by vacuum filtration to 68% yield. When dried, this powder possessed a sharp melting point (102.5 °C to 103.5 °C). ^1H NMR: δ 3.08(s, 2.78 H), δ 3.31(s, 2.84 H), δ 3.81(s, 3.00 H), δ 6.55(s, 0.76 H), δ 6.66(d, 0.74 H), δ 6.90(d, 0.88 H), δ 7.30(m, 10.0 H); Anal. for $C_{22}H_{22}O_4$. Calcd: C, 75.41; H, 6.33. Found: C 75.28%; H 6.01%

4. Phenylisocyanate Derivative of 1,2,4-TMS

At 25°C, one molar equivalent of n-BuLi was added to one molar equivalent of 1,2,4-TMB in hexane solvent and quenched with excess phenylisocyanate after 1.5 hours. Workup with Na_2CO_3 and hexane ensued, two layers formed and the organic layer was removed with a separatory funnel. Evaporation of the hexane solvent from the organic layer produced a conglomeration of sticky off-white product. Use of ethanol for fractional recrystalization afforded a 70% yield of white fiber-like crystals. These crystals also exhibited a sharp uncorrected melting point range of 149.5-150.8°C. ^1H NMR: (δ 3.75(s), δ 3.80(s) and δ 3.85(s)(9.0 H)) and (δ 6.60(d), δ 6.87(d), δ 7.15(t), δ 7.35(t), 7.58(s) and 7.70(d)(7.80 H); ^{13}C NMR: δ 56.41, δ 56.57, δ 62.01, δ 106.61, δ

114.13, δ 119.74, δ 119.93, δ 124.43, δ 128.93, δ 129.08, δ 138.17, δ 147.12, δ 150.87, δ 163.33; Anal. for $C_{16}H_{17}NO_4$. Calcd: C, 66.89; N, 4.86. Found: C, 66.55%; N, 5.14%

Table 8. Summary of Relevant o-DMB Runs and Their Conditions.

1) Equivalent Amounts of TMEDA at 0.04 mol/eq in 30 mL Ether and 25°C

Run Number	Percent Yield*	Time*	Amount of Catalyst
PS133	55%	30min	0.0 eq.
PS70	49%	2 min	0.05 eq.
PS134	61%	30 min	0.05 eq.
PS71	50%	45 min	0.1 eq.
PS120	58%	30 min	0.1 eq.
PS121	60%	30 min	0.3 eq.
PS122	59%	2 min	0.5 eq.
PS123	60%	30 min	1.0 eq.
PS135	34%	2 min	1.5 eq.
PS136	44%	10 min	2.0 eq.

2) Equivalent Amounts of TMEDA at 0.04 mol/eq in 30mL Hexanes and 25°C

Run Number	Percent Yield	Time	Amount of Catalyst
PS124	60%	2min	0.05 eq.
PS108	77%	6hr	0.1 eq.
PS112	69%	6hr	0.1 eq.
PS118	82%	2hr	0.3 eq.
PS119	65%	2hr	0.3 eq.
PS126	64%	10min	0.3 eq.
PS109	88%	6hr	0.5 eq.
PS113	74%	6hr	0.5 eq.
PS127	75%	2min	0.5 eq.
PS87	82%	30min	1.0 eq.
PS110	86%	4hr	1.0 eq.
PS114	71%	1hr	1.0 eq.
PS88	77%	30min	2.0 eq.
PS111	73%	2min	2.0 eq.
PS115	69%	10min	2.0 eq.

3) Equivalent Amounts of TMEDA at 0.04 mol/eq in 30mL Cyclohexane and 25°C

Run Number	Percent Yield	Time	Amount of Catalyst
PS116	80%	4hr	0.05 eq.
PS117	78%	6hr	0.1 eq.
PS154	76%	4hr	0.1 eq.
PS159	70%	2hr	0.3 eq.
PS161	71%	4hr	0.3 eq.
PS163	68%	6hr	0.3 eq.

PS165	80%	4hr	0.5 eq.
PS167	80%	6hr	0.5 eq.
PS171	82%	6hr	0.5 eq.
PS173	74%	6hr	1.0 eq.

4) 0.04 mol/eq in 30mL Cyclohexane at 25°C

Run Number	Percent Yield	Time
PS97	73%	24hr
PS155	70%	6hr
PS162	73%	2hr
PS166	74%	6hr

5) 0.04 mol/eq in 30mL Toluene at 25°C

Run Number	Percent Yield	Time
PS56	72%	4hr
PS290	70%	30min
PS291	81%	2hr

4) 0.04 mol/eq in 30mL MTBE at 25°C

Run Number	Percent Yield	Time
PS199	80%	1hr
PS245	82%	4hr
PS246	76%	30min

Table 9. Summary of Relevant m-DMB Runs and Their Conditions.

1) 0.04 mol/eq in 30mL hexanes at 25°C

Run Number	Percent Yield	Time
PS220	74%	6hr
PS233	71%	4hr
PS234	71%	4hr
PS276	67%	4hr

2) 0.04 mol/eq in 30mL hexanes at 45°C

Run Number	Percent Yield	Time
PS215	87%	4hr
PS223	81%	6hr
PS224	75%	6hr

3) 0.04 mol/eq in 30mL hexanes at 60°C

Run Number	Percent Yield	Time
PS247	85%	4hr
PS248	89%	1hr

Table 10. Summary of Relevant 1,2,4-TMB Runs and Their Conditions.

1) 0.02 mol/eq in 30mL Cyclohexane at 25°C

Run Number	Percent Yield	Time
PS195	86%	2min
PS207	91%	1hr
PS257	89%	2min
PS258	86%	2min
PS280	80%	10min
PS281	91%	10min

2) 0.02 mol/eq in 30mL THF at 25°C

Run Number	Percent Yield	Time
PS208	78%	30min
PS251	77%	4hr
PS287	81%	1hr

3) 0.02 mol/eq in 30mL Toluene at 25°C

Run Number	Percent Yield	Time
PS209	78%	30min
PS249	80%	10min
PS250	75%	1hr

4) 0.02 mol/eq in 30mL MTBE at 25°C

Run Number	Percent Yield	Time
PS225	87%	6hr
PS226	90%	4hr
PS286	80%	1hr

5) 0.02 mol/eq in 30mL Diethylether at 25°C

Run Number	Percent Yield	Time
PS288	73%	30min
PS289	82%	1hr

Table 11. Summary of Relevant 1,3,5-TMB Runs and Their Conditions.

1) 0.02 mol/eq in 30mL Hexanes at 25°C

Run Number	Percent Yield	Time
PS182	4%	2hr
PS190	0%	Entire Reaction

2) 0.02 mol/eq in 30mL Hexanes at 45°C

Run Number	Percent Yield	Time
PS218	13%	1hr

3) 0.02 mol/eq in 30mL THF at 25°C

Run Number	Percent Yield	Time
PS269	83%	1hr
PS270	85%	1hr

Table 12. Summary of Relevant 1,2,3-TMB Runs and Their Conditions.

1^{st} product = TMS derivative: 2^{nd} product = substitution product

1) 0.02 mol/eq in 30mL Hexanes at 25°C

Run Number	Percent Yield	Time
PS204	1^{st} product = 71% 2^{nd} product = 16%	1^{st} product = 30min 2^{nd} product = 4hr
PS213	1^{st} product = 54% 2^{nd} product = 11%	1^{st} product = 6hr 2^{nd} product = 30min
PS214	1^{st} product = 52% 2^{nd} product = 33%	1^{st} product = 4hr 2^{nd} product = 30 min

2) 0.02 mol/eq in 30mL Cyclohexane at 25°C

Run Number	Percent Yield	Time
PS189	1^{st} product = 55% 2^{nd} product = 32%	1^{st} product = 24hr 2^{nd} product = 24hr
PS205	1^{st} product = 73% 2^{nd} product = 13%	1^{st} product = 4hr 2^{nd} product = 30min
PS211	1^{st} product = 71% 2^{nd} product = 35%	1^{st} product = 6hr 2^{nd} product = 1hr
PS212	1^{st} product = 63% 2^{nd} product = 33%	1^{st} product = 6hr 2^{nd} product = 30min

3) 0.02 mol/eq in 30mL Toluene at 25°C

Run Number	Percent Yield	Time
PS305	1^{st} product = 36% 2^{nd} product = 19%	1^{st} product = 30min 2^{nd} product = 2hr

4) 0.02 mol/eq in 30mL THF at 25°C

Run Number	Percent Yield	Time
PS255	1^{st} product = 60% 2^{nd} product = 2%	1^{st} product = 30min 2^{nd} product = 30min

5) 0.02 mol/eq in 30mL MTBE at 25°C

Run Number	Percent Yield	Time
PS301	1^{st} product = 49% 2^{nd} product = 7%	1^{st} product = 2hr 2^{nd} product = 4hr
PS302	1^{st} product = 52% 2^{nd} product = 7%	1^{st} product = 6hr 2^{nd} product = 4hr
PS304	1^{st} product = 50% 2^{nd} product = 6%	1^{st} product = 6hr 2^{nd} product = 2hr

6) 0.02 mol/eq in 30mL Ether at 25°C

Run Number	Percent Yield	Time
PS303	1^{st} product = 48% 2^{nd} product = 6%	1^{st} product = 2hr 2^{nd} product = 2hr
PS306	1^{st} product = 53% 2^{nd} product = 6%	1^{st} product = 4hr 2^{nd} product = 2hr

All of the previous entries were carried out with one equivalent of n-BuLi.

* The percent listed in the second column is the maximum extent of metalation for a reaction. That sample was taken at the time listed in the third column.

IV. ABBREVIATIONS

ASN-	Aromatic Nucleophilic Substitution.
CIPE-	Complex Induced Proximity Effect.
ClTMS-	Chlorotrimethylsilane.
DMB-	Dimethoxybenzene.
DMF-	Dimethylformamide
DMG-	Directing Metalation Group.
EAS-	Electrophilic Aromatic Substitution.
GC-	Gas Chromatography.
MMB-	Multi-methoxybenzene
MTBE-	Methyl *tert*-Butyl Ether.
NMR-	Nuclear Magnetic Resonance.
PMDTA-	Pentamethyldiethyltriamine.
Sn_2-	Bimolecular Nucleophilic Substitution.
THF-	Tetrahydrofuran.
TMEDA-	Tetramethylethylenediamine.
TMB-	Trimethoxybenzene.
TMS-	Trimethylsilyl Group.
VPC-	Vapor Phase Chromatography.

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